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Vol. I. JANUARY, 1930 No. 2

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THE JOURNAL OF ALLERGY

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OFFICIAL ORGAN OF
THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE ASSOCIATION FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD,
ST. LOUIS, U. S. A.

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The Journal of Allergy

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The Journal of Allergy

VOL. I JANUARY, 1930 No. 2

Original Articles

ALLERGY IN ITS RELATION TO BEE STING*†

ROBERT L. BENSON, M.D.
AND
HERMAN SEMENOV, A.B.
PORTLAND, ORE.

THE harmful effects of bees are extremely complex and require consideration under three heads:

1. The venom of the bee sting, complicated in itself.
2. Allergic reactions in the human, caused by pollen adhering to the bee.
3. Allergic reaction in the human, from sensitization to allergens inherent in the bee.

The first of these factors appears with varying intensity in all instances of stinging by bees or other hymenoptera and is presumably general and nonspecific. The second is an incidental phenomenon in individuals who have become sensitized to the pollens of plants and is likely to be experienced on contact with bees laden with these pollens. The third factor, which forms the incentive for this report, has received little attention and concerns certain isolated examples of violent reactions in individuals stung by bees, and results from a specific allergic sensitiveness to bee protein. We shall review each of these factors briefly in its turn and then recite our own experience in the study of bee allergy.

1. BEE VENOM

The medical literature contains many reports on poisoning from bees, beginning with a study of bee venom in 1833 by Brandt and Ratzeburg[1] who liken it to viper poison. These early workers found that venom was bitter to the taste, soluble in water but not in alcohol and that it evaporated to form a tenacious gummy residue. Langer,[2] who deserves credit for having made the first thorough chemical examination of bee

*Read before the Seventh Annual Meeting of The Association for the Study of Allergy, July 8, 1929.

†From the Department of Pathology, University of Oregon Medical School.

venom, reviewed the early contributions. According to this author the poison apparatus of the bee is a highly complex mechanism.

Langer obtained venom from the honeybee by seizing the insect with two fingers, pressing its abdomen until the stinger was thrust outward, bearing on its tip a clear droplet of the secretion. These droplets from thousands of bees he collected in water and with this solution worked out the properties of what he termed true bee poison. He found the fluid water-clear and of acid reaction. Evaporation gave a residue resembling gum arabic in appearance. He observed that formic acid, which had been considered by earlier writers to be the active principle of bee venom, was not present in the potent residue obtained by distillation. The absence of formic acid from bee venom has also been repeatedly confirmed by others. Langer attributed the poisonous action of venom to a nonvolatile, protein-free, organic base. On the other hand Arthus[3] and Lyssy[4] believe that bee venom is a proteotoxin, and Flury[5] concluded that Langer's protein-free constituent is not a simple base but a complex one, from which he has isolated the following compounds:

1. An indol derivative, probably tryptophan.
2. Choline.
3. Glycerol.
4. Phosphoric acid.
5. Palmitic and other fatty aids.
6. A nonnitrogenous constituent having an action suggesting saponin.

This last named derivative contains the pharmacologically active principle of bee venom. Its neutral combination, presumably a cyclic acid anhydrid, produces inflammation when applied to the skin, while its corresponding acid causes hemolysis. The results of Flury suggest to Wells that bee poison represents a combination of lecithin with basic radicals, resembling in some respects sapotoxins and cantharadin.

The question here arises whether the recent results of Lewis[6] and his coworkers may not offer something to the study of bee stings. These authors conclude that certain forms of physical and chemical stimuli release in the skin a chemical substance, presumably histamine, that acts directly on the vessels and nerve endings to produce the wheal and vascular flare. Possibly the saponin-like substance in bee venom may serve in some such manner as a dermolysin releasing the histamine locally present in skin.

Indeed, we consider it highly probable that bee venom itself may contain a histamine-like substance. Prompted by the similarity of action of histamine and bee venom we have undertaken a comparison of these by the biologic and chemical methods. We find that the virgin guinea pig uterus is stimulated by one part of bee venom in a hundred thousand parts of Sollman's modification of Locke's solution. The curve thus obtained is similar to a histamine control run on the same

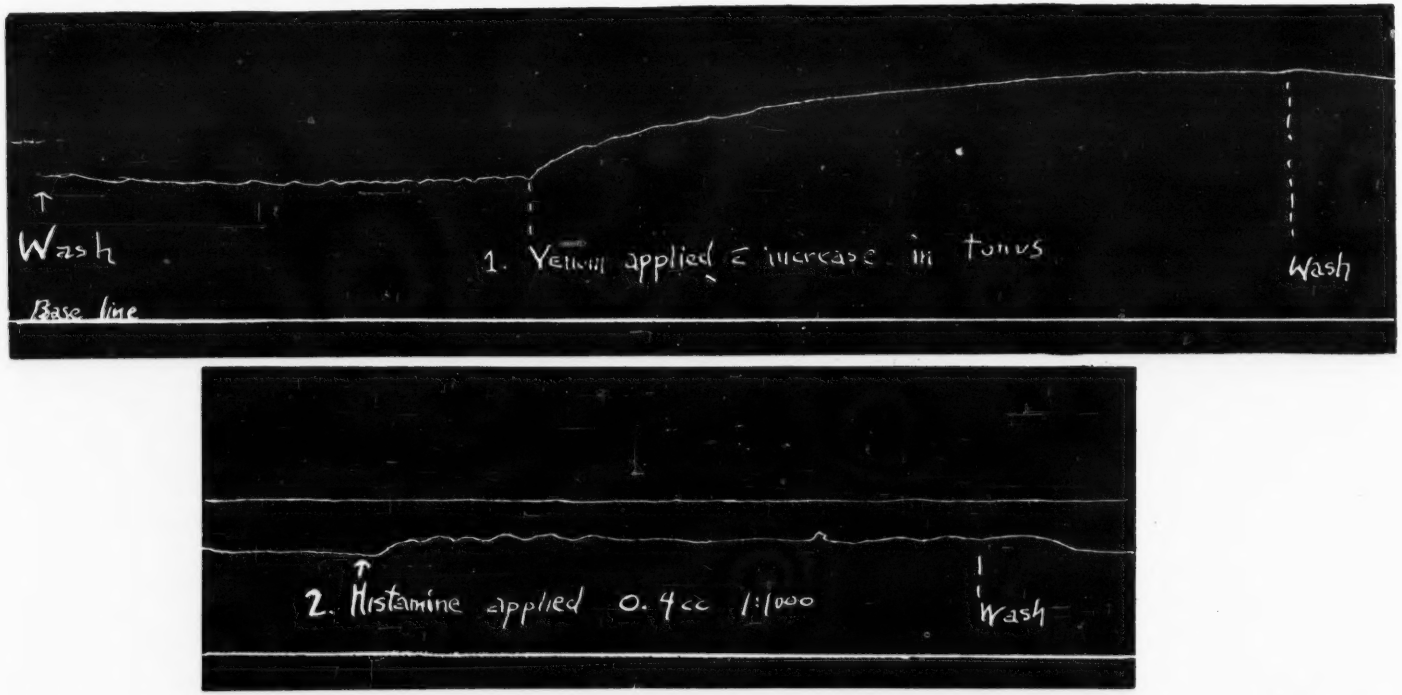

Fig. 1.—The first curve shows the effects of bee venom 1:100,000 solution applied on a virgin guinea pig uterus. The second curve shows the effects of the same amount of histamine phosphate applied to the same strip of uterus after washing out the venom solution.

strip of uterus. (See Fig. 1.) The active principle in bee venom, like histamine, is not destroyed by boiling or drying. According to our chemical tests of bee venom, using the method of Koessler and Hanke[7] an imidazole is present, but the amounts of venom used in our work have not been sufficient to enable us definitely to isolate and identify histamine. This requires further work.

2. ALLERGIC REACTIONS DUE TO POLLEN CARRIED BY BEES

It has been adequately shown by those who are familiar with the habits of bees, that the anatomy of these insects adapts them in a special manner to the carrying of considerable quantities of pollen. It has also been observed by others, as well as by ourselves, that cutaneous allergic reactions can be produced experimentally by testing certain pollen-sensitive individuals with extracts from bodies of bees. Nor is it necessary to demonstrate that allergic manifestations in the human may be caused by pollen from this source. The etiologic importance of such a relationship is, however, overrated in certain instances. For example, Gibb[8] reported hay fever, asthmatic symptoms and urticaria in a girl of seven years following bee sting, and concluded on immature evidence that "the bee had by its sting injected into the child a pollen to which she was sensitive," thereby producing the allergic symptoms. Such a possibility is at the best remote, even in the presence of known sensitization to pollens, and discounts too greatly the inherent action of the bee venom itself and of bee protein. It has not been proved that hymenoptera, in the process of stinging, do actually inject an appreciable quantity of pollen. In fact, our own microscopic study of bee stingers, and our observations on the mechanism of the protrusion of the sting shaft, have led us to believe that the lancet of the bee is almost entirely free from contamination with pollen. We shall also present some evidence here to indicate that an entirely different allergic factor may come into play, namely, sensitization to proteins inherent in both the body and the secretion of the bee.

3. ALLERGIC REACTION IN THE HUMAN, FROM SENSITIZATION TO ALLERGENS INHERENT IN THE BEE

The literature on this subject includes several instances of supposed anaphylaxis or allergy resulting from bee stings. The older references appear to be of slight value and are omitted from this discussion. Waterhouse[9] reported development of sensitiveness in a beekeeper who had previously had only the normal reaction to bee stings. Sensitization increased with each sting. Finally, on one occasion, a sting on the right ear resulted within a few minutes in difficult breathing and a sense of constriction about the throat. Ten minutes after the bee sting, the keeper collapsed and lay on the floor in a semiconscious, restless state with occasional sighing respirations. The pulse and heart sounds

were feeble, and there was perspiration associated with coldness of the extremities. Relative recovery occurred within three-quarters of an hour, and on the following day the heart action was normal. This author attributes the reaction to anaphylaxis.

Ewing[10] recorded similar observations in beekeepers. Hubert[11] reported a transient coma resulting from two wasp stings an hour apart and believes, in spite of the great proximity of the two accidents, that the patient had become sensitized by the first sting. Mantoux[12] also described anaphylaxis from wasp stings, and Goss[13] recounted his own personal experience with the development of an anaphylactic state due to bee sting. He also referred to other related cases. In all these cited references the evidence of anaphylactic sensitization rests on insecure ground and lacks confirmation of specific tests. The nearest approach we have found of specific sensitization is contained in the report of Braun[14] who observed severe symptoms from a bee sting in a female patient who had been stung seven times on previous occasions with increasing severity of the effects following each sting. On the last occasion, symptoms developed within a minute after the sting. The face became suffused and a hot flush went over the whole body accompanied by a choking sensation and coughing. Swelling of the neck and face was soon followed by intense "bearing down pains resembling labor." Extreme mental anxiety, choking sensation and generalized tremor compelled her to lie down. She soon passed into a state of coma, which lasted three or four days. This type of reaction recurred following subsequent encounters with bees. The author stated that complete protein sensitivity tests yielded no positive reactions. He did not, however, mention having tested with the bee proteins. A course of peptone and intravenous calcium therapy was tried but a later bee sting proved the inefficacy of this treatment. Adrenalin on the other hand was beneficial. Braun then resorted to repeated inoculation with increasing doses of bee extract made from the posterior eighth inch of the bee's body. After a course of this treatment he reported that a bee sting caused only mild symptoms.

The foregoing report bears evidence of a successful partial desensitization to the sting of bees and apparently excludes pollen as an exciting agent in the symptomatology. It is unfortunately lacking in specific tests for sensitization to bee protein, and fails to eliminate the possibility that the poison fraction of bee venom may be the cause. The symptoms recited by this author resemble histamine poisoning closely. The increasing sensitization to bee sting does point to the probability of an anaphylactic process, and further support for this theory is furnished by his observation that adrenalin gave definite relief. Attention must be called here to the fact that Wells[15] ascribed a histamine-like action to bee venom itself, and that adrenalin is a natural antagonist of histamine. We are, therefore, unable to conclude

positively that this writer obtained a desensitization to anaphylactogens rather than to the active principle of bee poison.

PRESENT STUDY

The incentive for the present study arose about three years ago when a beekeeper came to one of us complaining of hay fever which he attributed to bee stings. These attacks came in April, May, or even as late as June, and lasted until October. The beginning of each season's hay fever course started with the time when he began working with his swarms and endured with acute exacerbations following stings until the bee season closed.

When he first started keeping bees, about eighteen years before, his health was good; and during his first year he suffered numerous stings, as high as seventy-five in one day, with no recollection of

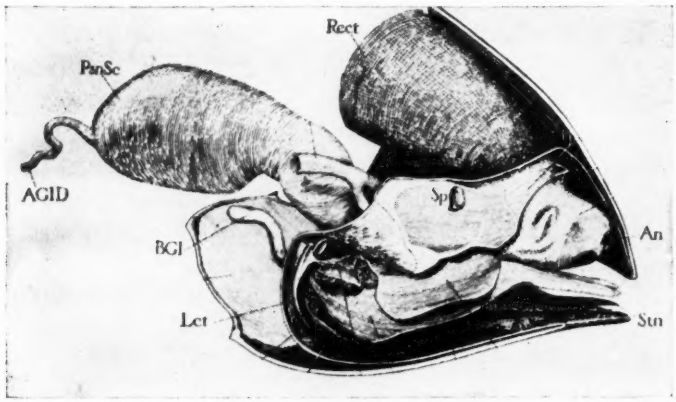

Fig. 2.—Sting chamber in rear of bee's abdomen showing the relationship of the acid gland, AGlD; the poison sac, PsnSc; the alkaline gland, BGl; the lancet, Lct; the tip of the stinger, Stn.; rectum, Rect; and the anus, An. After Snodgrass, *Anatomy and Physiology of the Honey-Bee.*

unusual consequences. During his second year he began to experience increasing distress with each sting. By the end of his third year, he developed such serious illness after a bee sting that he considered discontinuing the bee business.

The sting of a single bee, at that time, was immediately followed by irritation of the mucous membranes of the eyes and nose with violent sneezing and obstruction in the nasal passages. The acute attack generally cleared up in a day or two. Frequently a greenish nasal discharge was noted on the following day. During the last few years the symptoms following bee stings became worse. Some attacks simulated asthma with difficult respiration and consequent loss of sleep. One occasion was so severe that the patient thought he had pneumonia. Some stings were said to have caused his face to become blue.

To evaluate properly the possible factors in the causation of this complex of symptoms, it becomes necessary to revert to our primary

classification of the harmful effects of bee stings, namely, the toxic actions of bee poison proper, allergy to pollens carried on the bee, and allergic reactions to bee protein itself.

It is evident that a similarity in the symptomatology produced by these factors complicates the situation. For this reason carefully controlled skin tests were undertaken. It was decided to collect the venom of the bee, split it into its constituent parts and in this manner separate the pharmacologic agents. Inasmuch as it has been shown that bee venom contains considerable protein, it was thought that this could be precipitated and purified for use in skin testing. This was impractical because each bee secretes only about 0.0001 gram of pure venom, and the yield of absolutely pure protein, free from absorbed poison, is too small. It was therefore decided to extract bee proteins from the detached stinging mechanism of the bee.

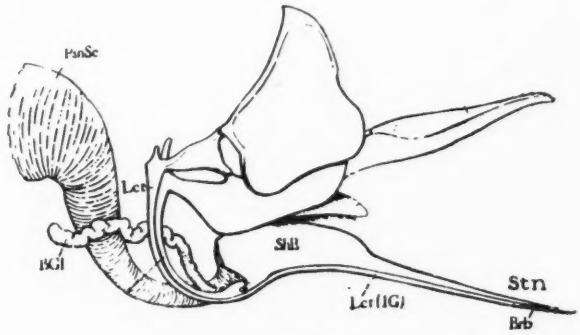

Fig. 3.

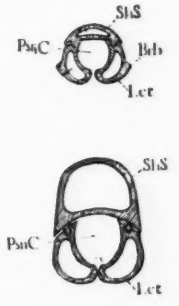

Fig. 4.

Fig. 3.—The isolated stinging mechanism of the bee. PsnSc, poison sac; BGl, alkaline secreting gland; Lct, lancet; Stn, stinger; Brb. barbs. After Snodgrass, *Anatomy and Physiology of the Honey-Bee.*

Fig. 4.—Cross-section of sting shaft showing the poison canal, PsnC; in the sting shaft, ShS; and the compartments for the two lancets, Lct. After Snodgrass. *Anatomy and Physiology of the Honey-Bee.*

STINGING MECHANISM OF THE BEE

A brief description of the poison apparatus of the honey bee as given by Snodgrass[16] might be of value here.

The sting is situated in the sting chamber at the rear of the abdomen (Fig. 2) from which it can be quickly protruded when occasion demands, the sting and accessories, including the poison sac, being left behind in the victim's flesh. The sting consists of a straight, tapering barbed shaft (Fig. 3) with its point directed posteriorly and its base swollen into a bulb-like enlargement, ShB. At first sight the shaft appears to be solid, but further examination shows it in reality to be composed of two distinct hollow darts lying side by side, and separated by a tubular space, the poison canal, PsnC (Fig. 4). Each dart slides in a track of its own on a common sheath shaft, ShS, which is also hollow.

The poison gland system is double, consisting of a small alkaline

gland, BGl, (Fig. 2) and a larger coiled acid gland, AGlD, which opens into the large poison sac, PsnSc. The secretion of the two glands is poured into the bulbous base of the poison canal, whence it is expelled during the stinging act by a valve-like structure on each dart. The acid secretion supposedly mixes with the alkaline secretion to form the poison that is injected with the sting.

PREPARATION OF MATERIALS

For purposes of study the bee material was divided into three component parts:

1. Venom.
2. Sting apparatus including poison sac.
3. Body (without sting apparatus).

To separate the poison system from the body of the bee the following procedure is used: The bee is caught between the fingers as it emerges from a small opening in its cage. When the stinger is projected, the lancet is grasped with a pair of cilia forceps, and the entire stinging mechanism with the poison sac and glands is readily separated from the body of the bee. After removal an active pumping action continues in the detached stinging mechanism, driving the venom toward the tip of the lancet where a clear drop soon forms. The droplets are collected from the tips of the stings on a glass cover slip, and these constitute the pure, natural venom. By immediately separating the extruded stinger from the body of the bee in the above manner, the possibility of contamination with pollen is minimized. Each bee yields about 0.0001 gram of venom. The stingers carry with them the poison sacs and glands and constitute the source of our stinger protein. The body of the bee from which the poison apparatus has been removed is utilized as the source of the stingerless body protein.

We assume on the authority of Langer that there is no venom action in the body of the bee after removal of the poison system. He says that the poisonous fluid voided by the sting is a specific secretion of the poison gland and that in no other organ of the bee has he been able to demonstrate such a poisonous action.

Preparation of Protein.—Protein from the bee sting mechanism is prepared in the following manner: The bee stingers with adhering poison gland systems, having been detached by cilia forceps, are collected to the number of several thousand. These are dried, ground, etherized to remove fats, and extracted for twenty-four hours. The fluid extract thus obtained, when treated to saturation with magnesium sulphate, yields a precipitate representing the contained protein of the bee stinger apparatus.

Dialysis for thirty-six hours gives two fractions, soluble and insoluble, respectively, the albuminous fraction and, presumably, the

globulin fraction. The stingerless bee bodies are treated in the same manner by drying, etherizing, extracting, and dialysing. This yields water-soluble and insoluble fractions of bee body protein, including necessarily some protein from adherent pollen. We now have the following products for testing:

1. Pure bee venom.
2. Protein from bee sting mechanism carrying with it some venom protein.
3. Protein from bee bodies and adherent pollen.
4. Isolated pollens, of types ordinarily used in testing.
5. Protein from honeycomb prepared by method similar to that for bee.

In the following skin test, protein solutions 1:100 were applied by the cutaneous method with a superficial scratch about 3 mm. in length.

PRELIMINARY TEST SEPTEMBER 26, 1927

	PATIENT	CONTROL
1. Bee stinger protein Water soluble fraction	4+, 15 mm.	1+
2. Water insoluble fraction	1+	trace
3. Bee protein from stingerless bodies, water soluble	4+, 14 mm.	negative
4. Honeycomb protein	1+	negative
POLLENS		
5. Velvet grass (Holcus lanatus)	3+	negative
6. Quack grass (Agropyron repens)	2+	negative
7. Ray grass (Lolium perenne)	2+	negative
8. Italian rye grass (Lolium multiflorum)	2+	negative

It is evident that the patient exhibits a high degree of sensitiveness to bee proteins as compared with the control subject. It is probable that there is a slight amount of venom adsorbed to the stinger proteins, and this accounts for the slight reaction in the control. Apparently the water-soluble fraction of bee protein is the active protein allergen because it gives the greater reaction. The patient is definitely sensitive to the stinger protein and reacts strongly to the body protein as well. Some of this action may be ascribed to pollens adherent to the body of the bee. The extent to which pollen figures in the total reaction can only be conjectured from other reactions. Thus the honeycomb protein, which is known to contain much of the pollen carried by bees, gives a one-plus reaction; while several pure pollen extracts

SEPTEMBER 30, 1928

	PATIENT	CONTROL
1. Venom raw	4 plus, 22 mm.	1 plus, 5 mm.
2. Venom boiled	3 plus, 15 mm.	1 plus, 5 mm.
3. Stinger protein raw	4 plus, 20 mm.	negative
4. Stinger protein boiled	2 plus, 9 mm.	negative
5. Vaughan's split protein	1 plus	1 plus
6. Histamine 1:1000	2 plus	2 plus

give reactions varying from one to three-plus. It is, therefore, possible to conclude that the patient exhibits an especial sensitiveness to inherent bee proteins in addition to his known reactions to pollens.

Further tests were made to gain additional information concerning the activity of the protein in bee venom. According to Flury[5] the poisonous principle in venom is a saponin which resists boiling and loses none of its activity. The question now arises whether boiling will affect the protein reactions.

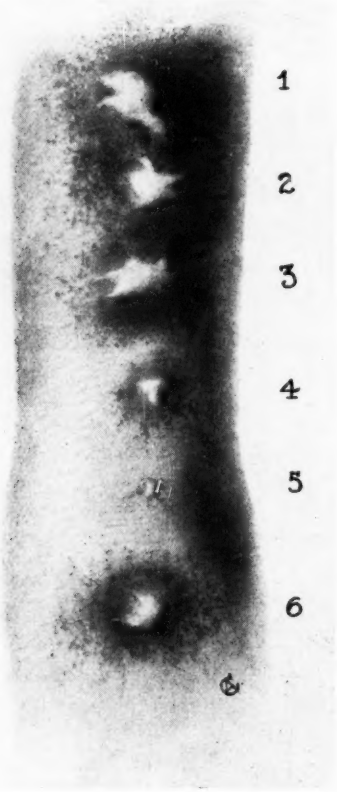

Fig. 5.—Reactions obtained on patient sensitive to bee proteins: 1, raw venom; 2, boiled venom; 3, stinger protein raw; 4, stinger protein boiled; 5, Vaughan's split protein; and 6, histamine control.

A solution of bee venom (1:100) was divided into two parts, one of which was boiled for five minutes. The same procedure was applied to a solution of bee stinger protein. The unboiled solutions were clear, but after heating a white precipitate was formed.

Fig. 5 gives a good impression of the relative values of these reactions. As expected in view of Flury's statement, venom reacts similarly in either the raw or boiled stage when applied to the control subject. On the other hand, stinger protein gives larger reactions when applied in the unheated form to the patient. If the activity of some of the bee

proteins is decreased when precipitated by heating, we can conclude from our results that the subject is definitely sensitive to bee protein.

A solution of 1:1000 histamine in saline and Vaughan split product of egg protein were applied for comparison. The reactions to these nonspecific agents were equal and similar in both the patient and the control subject.

Other confirmatory tests were made at various times, and these results in no way differed from those obtained above. Further pollen tests were also made at a later time and revealed the fact that the patient was sensitive to an extensive list of grass pollens. A number of other individuals, allergic and otherwise, were tested in a similar manner.

The nonallergic individuals give results that are uniformly negative to the bee proteins. An instance of such response is present in the control used above, Mr. H. S.

Treatment.—An attempt was made to desensitize the patient by specific inoculations. For this purpose 20 mg. of water-soluble bee stinger protein and 50 mg. bee body protein were dissolved in 7 c.c. of normal saline with the addition of 0.4 per cent phenol and filtered through a Berkefeld. This gave a dilution of 1:100 from which dilutions of 1:1000 and 1:10,000 were prepared. Starting treatment March 12, 1928, with 0.2 c.c. of 1:10,000 dilution, increasing doses were administered every two or three days by subcutaneous inoculation up to and including 0.8 c.c. of the 1:100 dilution.

The results have been entirely satisfactory. The patient states that on May 8, 1928, after completion of the second bottle, he received at least 25 stings with no ill effects other than a slight temporary discomfort. On June 14, 1929, more than a year after the administration of the bee solutions, the patient still felt that this desensitization had persisted. Bee stings had been received in considerable number at various times and had caused no unusual reaction. On this last date the authors observed a sting which the patient had encountered a few hours previously at the lateral canthus of the left eye. There was no noticeable reaction, and the patient stated it had caused him no unusual discomfort. Pollen treatment is being carried on for the present season, March 10, 1929, and results have been successful to a fair degree. His hay fever symptoms are mild and devoid of discomfort in the eyes and are attended by only slight nasal congestion. Sneezing is noticeably absent.

CONCLUSION

An attempt has been made to evaluate the relative importance of the three factors concerned in the harmful effects of bee stings, namely, bee venom poison effects, pollen effects, and allergic reactions to proteins intrinsic in the body and stinger of the bee. The presence of venom and pollen action is admitted and recognized. We have, how-

ever, partially succeeded through testing and treatment in demonstrating that allergy to intrinsic bee proteins exists in certain individuals and that it is amenable to specific desensitization. It is hoped that other cases may be handled in this same manner for comparison—especially those in which there is not a complicating factor of pollen sensitiveness.

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AN UNUSUAL OPPORTUNITY TO MAKE AN ALLERGIC STUDY OF AN ENTIRE COMMUNITY WITH THE ETIOLOGY AND RESULTS OF TREATMENT*

GEORGE PINESS, M.D., AND HYMAN MILLER, M.D.
LOS ANGELES, CALIF.

WE HAVE had the unusual opportunity recently to observe and control two complete communities for the study of their allergic problems. This we believe to be unique in the field of allergy, permitting a gathering and correlation of data approaching in accuracy that obtained in laboratory experimentation. Our laboratories are here two comparatively young communities. The larger has a population of 3000 and is about twelve years old, and the smaller with a population of about 1000 is ten years old. Both are company-owned and controlled, the larger a mining community and the smaller an industrial one recovering potash and borax from a salt lake. In the former it was long thought to be the smelter fumes which produced in the inhabitants the symptoms leading to our study, and in the latter it was thought to be the potash dust. The suspicion that the symptoms were due to hay fever rather than to chemical irritation grew out of the circumstance that from each of these communities we were treating an individual for hay fever. This led to our being called into consultation and the suspicion confirmed. Our report concerns the methods used in confirming this suspicion, the conclusions drawn therefrom, our mode of treatment and its results upon the inhabitants.

The mining community is situated at an elevation of 3500 feet along the banks of a small, permanent stream with surrounding plateaus, mountain slopes, dry mesas and alluvial flats. The average rainfall is 8 inches. The winter rainy season extends from December to March, and during the months of July and August heavy thunder showers occur over the mountains daily. The average temperature is about 65°. The maximum temperature is about 110° with very low humidity which leads to the presence of a superabundance of air-borne pollen.

The vegetation of this region is comprised of such native trees as alder, cottonwood, mesquite, soapberry and willow. With the cultivation of the alluvial flats and the establishment of lawns and a golf course, many plants such as Bermuda grass, ditch grass, salt grass, Russian thistle, chenopods, pigweeds, poverty-weed and salt-bushes have gained a foothold. A near-by lake, the river and the irrigation of

*Read before the Seventh Annual Meeting of The Association for the Study of Allergy, Portland, Oregon, July 8, 1929.

lawns furnish sufficient moisture for the maintenance of plant life capable of producing pollen from early spring until frost.

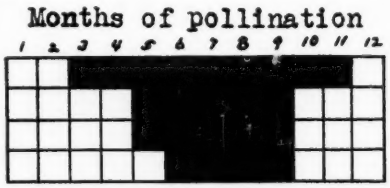
The botanical survey made by our botanist, Dr. H. E. McMinn, led us to the conclusion that Bermuda grass and Russian thistle because of their abundance and the prolonged duration of their pollinating season would prove to be the most important sources of pollen in this vicinity. Table I groups the pollinating plants in the order of their botanical importance and gives the pollinating dates. The pollinating season of the group as a whole extends from April to the first frost in November.

TABLE I

BOTANICAL SURVEY OF MINING COMMUNITY

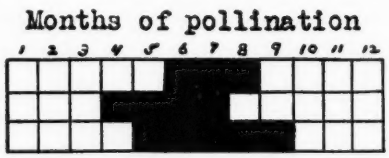
GROUP A. MOST IMPORTANT

Cynodon dactylon	(Bermuda grass)
Salsola kali	(Russian thistle)
Atriplex canescens	(Wingscale)
Atriplex rosea	(Redscale)



GROUP B. SECONDARY IMPORTANCE

Amaranthus palmeri	(Careless weed)
Distichlis spicata	(Salt grass)
Holcus halepensis	(Johnson grass)



GROUP C. SUPPLEMENTARY LIST. PLANTS WHICH ARE TOO SCATTERED OR RARE TO BE CONSIDERED FACTORS OF MUCH IMPORTANCE IN THIS REGION

Agrostis	Bromus	Franseria	Paspalum	Sitanion
Amaranthus	Celtis	Hilaria	Platanus	Sporobolus
Ambrosia	Chaetocloa	Hordeum	Populus	Stipa
Aristida	Chenopodium	Juglans	Polypogon	Urtica
Atriplex	Echinocloa	Koeleria	Quercus	Xanthium
Avena	Elymus	Lolium	Rumex	

The potash community is situated at an elevation of 1650 feet on the bank of a salt lake from which brine is being pumped for the recovery of the contained salts. The region is a desert one with an annual rainfall of somewhat more than 2 inches. The maximum temperature is about 126° with very low humidity making for the presence of a high concentration of air-borne pollen as in the mining community. The first frost occurs usually in the latter part of November or early in December.

The vegetation of this region is characteristically of the desert type with the saltbushes and alkali-blite as representative of the most important native plants. With the establishment of living sites and the planting of lawns and trees, Bermuda grass, salt grass and cottonwood, all of which are under irrigation, have become common in the immedi-

ate vicinity of the township and because of constant irrigation are capable of producing an abundance of pollen as a group from February to December as Table II shows.

Artemisia tridentata or mountain sagebrush is included in Table II because one must pass through an extensive area covered by this plant in order to reach the town site, and it is therefore an important factor in the production of hay fever in the inhabitants.

After the botanical surveys were completed, a census in the mining town gave us 133 hay fever patients. This in a population of 3000 gives a rate of 4.4 per cent, which is considerably higher than we had expected from the rates quoted in the literature. In the smaller community only 15 patients presented themselves for study, although the phy-

TABLE II

BOTANICAL SURVEY OF POTASH COMMUNITY

		Months of pollination 1 2 3 4 5 6 7 8 9 10 11 12
GROUP A. MOST IMPORTANT		
Cynodon dactylon	(Bermuda grass)	
GROUP B. SECONDARY IMPORTANCE		Months of pollination 1 2 3 4 5 6 7 8 9 10 11 12
Distichlis spicata	(Salt grass)	
Artemisia tridentata	(Sagebrush)	
Atriplex canescens	(Wingscale)	
Atriplex polycarpa	(Allscale)	
Suaeda depressa	(Alkali-blite)	
Populus fremontii	(Cottonwood)	

GROUP C. SUPPLEMENTARY LIST. PLANTS WHICH ARE TOO SCATTERED OR RARE TO BE CONSIDERED FACTORS OF MUCH IMPORTANCE IN THIS REGION

Atriplex	Franseria	Salicornia	Suaeda

sician in charge estimated that there were actually 30 to 40 present in the group, in which event the incidence rate would be about 3 per cent.

Although only 133 patients lived in the mining community, there were 156 studied, the additional patients coming from near-by territory. Our statistics from this point on, therefore, concern 171 individuals. Of these, 95 or 55 per cent were males, and 76 or 45 per cent were females. The preponderance of males is explained by the fact that both communities are industrial in character.

A history of positive heredity in parents was obtained in 52 cases or about 30 per cent. This is considerably lower than is usually expected and brings up the question of the relative susceptibility of allergic individuals with and without an hereditary history. As will be shown later, one is led to believe that in many instances a susceptible individual may go through life without symptoms unless overcome by an over-

whelming dose of pollen such as received by the members of both the communities here described. It is interesting to note that in 13 instances both husband and wife had hay fever. In six of these there was no heredity on either side. In the remaining seven heredity was positive on only one side. In the former only one family had a child as a patient, whereas in the latter group five families each had a child as a patient.

Perhaps the most interesting and significant finding in going over the histories of our patients is the fact that the great majority began to have hay fever only after moving to these vicinities. This was true in 111 or 71 per cent of the patients in the mining town and 12 or 80 per cent in the smaller town, certainly a remarkable number. In 97 instances we were able to determine how long the patient had lived in his

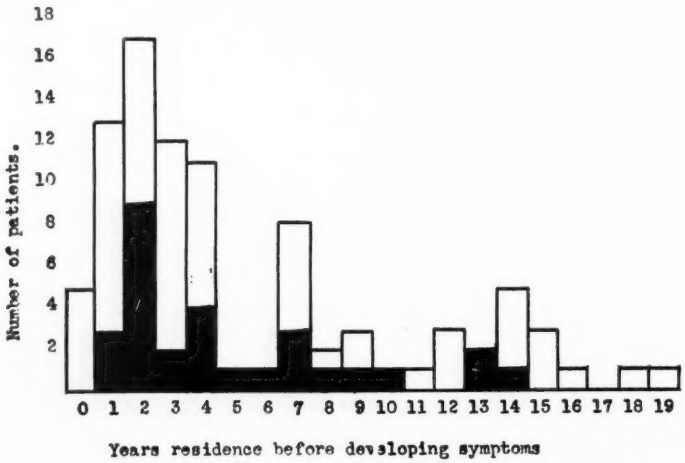


Chart I.—Shows number of patients developing symptoms for each year of residence. Shading indicates the proportion giving a positive hereditary history.

community before developing symptoms. This information is gathered and illustrated in Chart I, which shows that most of the patients developed symptoms within the first few years of their stay. It would seem, therefore, that a susceptible individual cannot for long withstand the sensitizing effect of a heavily pollen-laden atmosphere such as we find in these regions. Why some patients do not develop symptoms until after ten or fifteen years' exposure is not evident in the present state of our knowledge. We thought that heredity might be the deciding factor, and in Chart I we have shaded those portions which represent patients with positive heredity. Although the numbers are too small for critical evaluation, it would seem that heredity plays but little part in determining how long an individual must be exposed before developing symptoms. In fact this is so striking when taken into consideration with the low general incidence of positive heredity and the high incidence of hay fever that we have considered the possibility that even

nonallergic individuals, so called, may have become sensitized by the superabundance of pollen.

Chart II shows that symptoms usually develop in early life, although it should be noted that both communities are composed in the main of comparatively young individuals, thus modifying the age distribution in the groups under observation. The shaded portions of Chart II indicate the proportion of individuals in each age group having a positive heredity. It is seen that with onset in the first two decades of life a positive hereditary history is more common than later, and it would, therefore, seem that a positive hereditary history would tend to an earlier onset of symptoms.

Symptomatology need not be gone into here. Suffice it to say that it was characteristic of hay fever and that 21.6 per cent of the patients also had asthma. A number of those presenting themselves for exami-

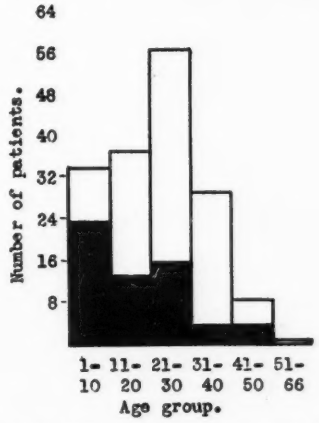


Chart II.—Shows number patients developing symptoms for each age group. Shading indicates the proportion giving a positive hereditary history.

nation were eliminated from the group for testing on being diagnosed as suffering from nonallergic ailments.

Testing was done with buffered glycerine salt extracts of pollen in the strength of 1-50 for scratch testing and 1-1000 for intradermal testing. Intradermal tests as a matter of precaution were done only after scratch tests were negative or doubtful. The pollen extracts used were only those which our botanical survey demonstrated as being of importance in the regions in which we were interested and were made from pollens collected in these regions.

Table III is arranged to show the correlation between the importance of each wind-pollinated plant as deduced from the botanical survey and its importance with regard to the frequency with which it gave positive skin reactions. That our deductions from the botanical survey were correct is evidenced by the fact that the botanically important Bermuda grass and Russian thistle in the larger community and Bermuda grass and salt grass in the smaller community gave by far the greatest

number of positive reactions. Only 9 patients gave no reactions, several of these having been only tentatively diagnosed as hay fever. On the whole, the skin reactions were graded as 4 plus, which we believe shows that the group being an untreated one had a high degree of susceptibility to pollen.

An attempt to correlate the pollinating dates of the positively reacting plants with the time incidence of symptoms in the individual led to no definite conclusions. This was to be expected, since all but 3

TABLE III

RELATION BETWEEN BOTANICAL IMPORTANCE AND FREQUENCY OF POSITIVE SKIN REACTIONS

MINING COMMUNITY			
		NUMBER OF REACTIONS	PER CENT
MOST IMPORTANT			
Cynodon dactylon	(Bermuda grass)	111	80
Salsola kali	(Russian thistle)	110	79
Atriplex canescens	(Wingscale)	63	45
Atriplex rosea	(Redscale)	78	56
SECONDARY IMPORTANCE			
Amaranthus palmeri	(Careless weed)	90	65
Distichlis spicata	(Salt grass)	48	35
Holcus halepensis	(Johnson grass)	38	27
139 patients gave positive skin reactions.			

POTASH COMMUNITY			
		NUMBER OF REACTIONS	PER CENT
MOST IMPORTANT			
Cynodon dactylon	(Bermuda grass)	15	100
SECONDARY IMPORTANCE			
Distichlis spicata	(Salt grass)	14	93
Artemisia tridentata	(Sagebrush)	9	60
Atriplex canescens	(Wingscale)	5	30
Atriplex polycarpa	(Allscale)	6	40
Suaeda depressa	(Alkali-blite)	9	60
Populus fremontii	(Cottonwood)	6	40
15 patients gave positive skin reactions.			

patients reacted to more than one pollen. Moreover, there were individual variations in tolerance and in degree of exposure, those doing indoor work being, of course, less exposed than those doing outdoor work. In the larger community the establishment of a golf course markedly increased the incidence of hay fever among the office workers, and in both communities the planting of lawns marked the beginning of hay fever in many of our patients. So far as season was concerned, it may be said that most patients began to have their symptoms in April or May and that symptoms continued until first frost, some time in November.

Treatment was administered, and the results were reported in 91 cases in the larger community and 14 in the smaller. Treatment was begun in January with 0.1 c.c. of a 1-50,000 pollen extract administered hypodermically and then increased in ascending doses at five-day inter-

vals until mid-April, the final dose being 0.5 c.c. of a 1-50 extract. The total dosage was then 33,330 pollen units given in 20 injections. It was occasionally necessary to administer treatment during the hay fever season, in which circumstance the dosage was usually kept constant, about 0.3 c.c. of a 1-5,000 solution.

Because of the close control kept over both groups, the results of treatment were capable of being almost exactly evaluated. In the larger community we received 91 reports. Of these 5 or 5.5 per cent were failures, 15 or 16.5 per cent obtained some relief and 71 or 78 per cent obtained good to complete relief. In the smaller community 15 patients were treated and 14 reports received. All fourteen results may be classed as practically complete to complete relief—in other words a result approaching 100 per cent.

SUMMARY

The successful outcome achieved in the care of the allergic problems of two entire communities we feel is the result of the following factors:

1. A thorough botanical survey of the regions involved.

2. A thoughtful summary of the symptomatology of the group as a whole with a correlation of the symptomatology and the botanical survey.

3. Well-controlled and thorough treatment with proper pollen antigens properly prepared.

(For discussion, see p. 177.)

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STUDIES IN THE ASTHMATIC STATE: I. THE STIMULUS*

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CLINICAL observation of bronchial asthma emphasizes the great variety of influences which seem to bring on attacks. Before the relationship of protein sensitization and allergy to asthma was studied, major importance was attributed to respiratory infection, disturbances in the nose, psychic and emotional disturbances, atmospheric and barometric conditions, and reflex stimulation from disturbances of the gastrointestinal tract and uterus. Since the introduction of the idea of allergy and protein sensitization, an attempt has been made to fit all bronchial asthma into an hypothesis whose major premise is that bronchial asthma is primarily a disease of allergy and that all other manifestations of the asthmatic state are secondary to this phenomenon.

Thus, Cooke[1] states that although almost all cases of bronchial asthma give as the apparent reason for their attacks a large and heterogeneous group of causes, he believes that they act only in those individuals in whom bronchospasm has become a habit as a result of some previously manifested allergic reaction. He believes that a hereditary disposition toward allergy exists and that the basis is a constitutional factor.

Alexander,[2] on the other hand, stresses the fact that only in recent years has bronchial asthma come to be looked upon as something more than an effect resulting from a single process, be that infection, psychic disturbances, nasal irritation, allergy, or mechanical irritation of the bronchi. He believes that a broader conception of the disease, although as yet imperfectly understood, is leading to a more exact understanding of the reactions involved and thereby offers a wider outlook for rational therapeutic measures.

The present study is concerned with the question of the stimulus to the asthmatic state. It will seek to evaluate the rôle of allergic and other classes of stimuli in the disease entity known as chronic bronchial asthma. As a result of the clinical study of asthmatics it will be shown that whereas the quantity and quality of stimuli vary widely, the end-reaction may be the same. It will also be indicated that the ultimate basis of the asthmatic state lies in neurophysiologic relationships, particularly those involving excitation of the vagus nerve and its reflex paths.

*From the Asthma Department of the Cornell Clinic, Cornell University Medical College, New York City.

Read before The Society for the Study of Asthma and Allied Conditions, Atlantic City, May 3, 1929.

The material for this study was obtained at the Asthma Clinic of the Cornell University Medical College and consists principally in facts gained from continued observation of twenty-five patients. As a general rule, the patients were selected only on the basis of a severe asthma. They represent for the most part patients who have had asthma for two years or more.

The stimuli leading to the initial attack of asthma in this series of cases could be narrowed into two classes: (first) an infection involving the respiratory tract, and (second) specific protein sensitization. Among 13 cases, an acute bronchitis, influenza, pneumonia, or acute sinusitis definitely preceded and led up to the first symptoms of asthma. In four cases, a definite history of hay fever preceded the first attack, and in the remaining eight cases a consideration of the history, environment, and skin tests pointed to a specific protein basis for the initial asthmatic attack.

When the stimuli leading to subsequent attacks were investigated, it was found that in most cases a wide variety of stimuli could lead to an attack of asthma. These stimuli have been divided into three groups:

(1) Specific protein stimuli,

(2) Infections involving the respiratory tract,

(3) Nonspecific excitants, including the heterogeneous group of atmospheric conditions, emotional and psychic states, exertion, irritants, digestive and uterine conditions.

Although the form of stimulus varied widely, no sharply differentiated form of asthmatic response was peculiar to any one of the three groups. The distinct asthmatic paroxysm, as well as the milder form of expiratory dyspnea, chiefly characterized by wheezing and expectoration, resulted at times from a stimulus in any one of the three groups of stimuli mentioned.

The interrelationship of the three groups of stimuli leads first to a consideration of the rôle of protein sensitization as a stimulus to the asthmatic state. At the Cornell Clinic the intradermal method of skin testing is used with protein extracts supplied by the Department of Immunology of the New York Hospital. In each case, the positive skin tests were noted. Then, by means of the history, elimination of the protein or the effect of the presence of this particular protein, on the asthmatic state, it was determined which protein or proteins seemed to be concerned with the patient's asthma. In 21 cases, extracts gave positive tests to proteins which seemed to represent stimuli to asthma. In only six cases did the absence or deprivation of the reacting protein stimulus or stimuli result in no asthma, or in very little. Thus in 15 cases known to have a specific protein as a stimulus to asthma, it was found that asthma occurred regardless of the presence or absence of particular protein stimuli.

The exact mechanism of respiratory infection acting as a stimulus to asthma may be largely at question. Yet, that the presence of an infection in the respiratory tract may initiate an attack or cause attacks of asthma to occur in an asthmatic is well known. In this series of asthmatics, respiratory infections and damage to the respiratory tract were evidenced in a number of cases from the nose and accessory sinuses down to the terminal bronchioles. In 15 cases, antral disease was indicated by transillumination, x-ray, or sinus washings. In 10 cases there was evidence of polypi or polypoid degeneration of the middle turbinates. A number of these cases were considerably improved or relieved of their asthma only after very complete drainage of the sinuses or removal of polypi. Acute tracheitis and bronchitis in almost every case caused at some time an asthmatic attack. The presence of a chronic infective bronchitis was hard to demonstrate absolutely, but in a large proportion of these cases—considering the frequency of repeated attacks of acute bronchitis and x-ray evidence of increased peribronchial markings—there seemed little doubt that such a condition existed and its presence was responsible for many attacks. Bronchiectasis was found in three cases by lipiodol injection of the bronchial tree. In these cases the alleviation of the asthmatic state was most difficult. In this series of chronic asthmatics respiratory infection was common and was accompanied by structural damage to the respiratory tract. As a stimulus to the asthmatic state, it played a very important part, regardless of whether the "primary" cause of the asthma was a specific protein or not.

To an asthmatic patient, the nonspecific group of excitants represent a class of very real stimuli. In only four patients in this series was reactivity to nonspecific excitants not marked at some time or other. Atmospheric conditions played a large and important rôle in bringing on attacks in all but four cases. Nonprotein irritants to the respiratory tract were considered as definite causes of asthma by ten patients. In eight patients indigestion, principally attributed to overeating, caused attacks. One patient was entirely free from asthma except during dysmenorrhea. In three patients, at least, fatigue brought on attacks and in practically all these patients at some time attacks were initiated by overexertion.

The influence of psychoemotional states such as nervous strain and nervous fatigue, depressions and worry were noted as important stimuli by thirteen patients. Striking examples of this might be cited. A patient who was sensitive to horse dander had improved greatly with elimination and injections of horse dander protein. However, during a period of six weeks when his father was seriously and hopelessly ill, the patient began to have asthma again. These attacks terminated shortly after the relief of the nervous tension that came with the death of his father. Another patient, sensitive to milk and dust, having been

greatly relieved of her asthma by elimination and specific treatment, again became asthmatic during the time she cared for her dying mother. In another patient, the influence of argumentation and aggravation of one sort or another was so obviously a stimulus to asthma that his whole family gradually accepted this and adopted tacitly a program of quiet and compromise with a marked diminution in the frequency of the patient's attacks. A final example of this is a patient whose asthma dated from ragweed hay fever. This patient was so asthmatic that he was placed in the wards of the New York Hospital. Here depression caused by another patient's dying, or excitement in the ward over a critically ill patient, as well as the nervous strain felt by the patient over increasing incompatability with his wife, were very real stimuli to asthmatic attacks long after ragweed pollen ceased to be in the air.

As a corollary of this study, an attempt was made to evaluate these three groups of stimuli in the order of their importance as factors in causing asthmatic attacks, by rating them as first, second or third. When this was done, it was found that protein stimuli ranked first in nine cases, second in two cases, and third in nine cases. Respiratory infection ranked first in fourteen cases, second in seven cases, third in two cases. Nonspecific excitants ranked first in two cases, second in thirteen cases, and third in six cases.

As a result of this study it seems evident that in these twenty-five representative cases of asthma, the stimuli to asthmatic attacks varied widely, but the result of the stimulus was usually the same; i.e., an asthmatic attack. At the present time it seems contrary to the important facts of clinical observations and to the results of the use of allergic methods, to attribute to bronchial asthma any one specific and embracing form of stimulus. Protein sensitization is of immense importance, but respiratory infection, nose and accessory sinus anomalies and the whole heterogeneous group of nonspecific excitants play likewise a very important part in exciting the asthmatic state.

Coca[3] has recently stressed the importance of shock tissue in atopic hypersensitiveness. In considering the relation of a shock tissue to the asthmatic state, the facts of neurophysiology point strongly to vagus nerve stimulation as playing the ultimate part in bringing it into action. A large amount of experimental work concerned with the stimulation of the vagus tends to prove that when this nerve or its reflex paths are properly excited, conditions approximating the asthmatic state in the lungs and bronchi can be produced. The work of Brodie and Dixon,[4, 5] who showed that stimulation of the vagus nerve and posterior portion of the nasal mucous membrane resulted in a rise of intratracheal pressure, which was abolished when the vagi were severed, is fundamental as is likewise that of Paul Bert,[6] Einthoven[7] and other investigators along the same line. Alexander and Paddock[8]

were definitely able to cause asthma in asthmatic patients by injecting pilocarpine with stimulation of the vagus nerve, and felt that a large proportion of asthmatics probably belonged to the clinical group which Eppinger and Hess,[9] Barker and Sladen,[10] Falta,[11] Petren and Thorling,[12] and Wilson[13] designated as vagotonic. More recently Mount[14] has made physiologic and histologic observations on dogs, guinea pigs and monkeys with regard to the symptoms and changes produced by various types of stimulation of the vagi in the neck. In many cases the resultant changes in the lungs, bronchial constriction, bronchorrhea, cellular infiltration and emphysema, were similar to those seen in asthma.

If it is granted that stimulation of the vagus or its reflex paths can cause asthma, it seems dangerous to imply that in the lung and bronchi, supplied as they are by such a profuse network of autonomic and sympathetic fibers, only allergy is at the root of bronchial asthma. In the gastrointestinal tract with its similar autonomic and sympathetic innervation, one finds a wide variety of stimuli that may excite the autonomic system. Pylorospasm may be cited as an example of a condition that may occur as a result of protein sensitization, ulceration of the pylorus, irritating substances in the stomach, psychic and emotional factors and reflex stimuli from other parts of the gastrointestinal tract or parts independent of it.

Concerning the irritative effect of protein stimulation on tissue and the possibility of this feature producing nervous excitation, one does not have to look further than the condition of the conjunctival mucous membrane in hay fever to see the irritative effect that allergy may have on tissue. Again it must be remembered that an infectious conjunctivitis or the presence of a foreign body in the eye may present almost the same picture. Likewise it is not necessary to assume that asthma as a response to respiratory infection is necessarily an allergic manifestation. It is almost an axiom of tissue physiology that within certain limits a damaged tissue is a more irritable one. In the chronic asthmatic, as has been shown, there is often evidence of damage to the respiratory epithelium from the nasal mucosa to the terminal bronchioles. Most often this damage seems to be the result of infection. With an infection in any part of the respiratory tract, there is reason to believe that the vagus may be stimulated to reflex activity as a result of the irritation or damage caused by the infection and not necessarily because of allergy. Certainly, it is difficult to enumerate many cases where chronic bacterial infection in the body at points outside the respiratory tract seems to cause asthma. Although there are numerous asthmatics who have chronic pyelitis, chronic urethritis, chronic furunculosis, etc., it is very rare in our experience to find that the lighting up of an infectious focus outside the respiratory tract gives rise to asthma either as the first attack or exerts a stimulus to

subsequent attacks per se. Likewise in our experience, it is comparatively rare, although undoubtedly it sometimes happens, to see an attack of asthma caused by the injection of an autogenous vaccine. When this does happen it is difficult to be sure of the specificity of the reaction.

The effect of the nonspecific excitants in causing asthma to a large measure seems to be due either to direct or indirect vagus stimulation on the basis of a conditioned reflex act. As has been said by Cooke,[1] "the bronchial mucous membrane and smooth muscle fibers of the bronchi have acquired the habit of reacting, and manifest this upon the slightest provocation from any irritation." If this is granted, it is difficult to maintain that with requisite lowering of the threshold irritability from any cause, any stimulus to bronchial spasm may not initiate the asthmatic state or cause an attack. However, in our experience, infection and protein sensitization had been sufficient to explain the initiation of the first asthmatic attack.

In conclusion, it is felt that the evidence of bronchial asthma as a fundamental expression of allergy, is not proved. The importance of various unrelated stimuli to the asthmatic attack points to an underlying neurophysiologic basis for asthma. The important hereditary and genetic factors in allergy as indicated by Cooke and Van der Veer,[15] Balyeat,[16] and Adkinson[17] may be related in bronchial asthma to a constitutional basis, particularly involving the autonomic nervous system and its receptors.

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MALARIAL URTICARIA AND ALLERGY*

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RECENT studies of intestinal parasitic infestation by means of cutaneous reactions indicate that individuals may be hypersensitive to parasites. This prompts the report of the following case of urticaria occurring as the result of malarial infection.

A white woman, married, age thirty-seven, was first seen by one of us (A. E. S.) on the morning of June 15, 1929. She was complaining of epigastric pain of such severity that ¼ grain of morphine was given for relief. She was then taken to the hospital.

The family history was unimportant save for a very questionable history of asthma in the mother.

The past history disclosed the fact that two years before the patient had had an attack of malaria associated with an ill-defined gastric disturbance manifested by dull epigastric pain with nausea and vomiting. This gastric disturbance has occasionally recurred. There was no known allergic condition; and no infections save measles during childhood.

Present illness. The patient left her home in Ridgely, Tennessee, on June 14, 1929, at 4 A.M. to proceed to St. Louis. About 9 A.M. she noticed a severe epigastric pain, which increased in intensity and which was associated with nausea, vomiting, and a chill, but with no fever. The pain became so severe that medical attention was obtained in a small town en route, with temporary relief. The patient continued on her way to St. Louis. The following morning (June 15) there was a recurrence of the epigastric pain with nausea and vomiting, this time without chill, but of such severity that morphine was given. The temperature and pulse were normal. Slight epigastric tenderness was noted but without rigidity or spasm; otherwise the physical examination was essentially normal. An acute gall bladder condition or an acute food upset was suspected and the patient was taken to the hospital. On admission the urine was negative; the white blood count was 17,400 with a normal differential count, and no malarial plasmodia were found. The course in the hospital was of particular interest and was as follows:

There was no further pain on day of admission. The temperature was 99.5°. However, the following morning at 8:30 there was a return of the severe epigastric pain with eructation and nausea. This was followed by a generalized giant urticaria and a temperature rise to 101.4° (rectal). Prompt relief of all symptoms was obtained by the intramuscular injection of adrenalin. Again, the next morning (June 17) there was a recurrence of the epigastric pain with generalized urticaria which was relieved by adrenalin. At noon the patient had a slight chill with fever. The generalized erythema and urticaria recurred and were again relieved by adrenalin intramuscularly. The white count at this time was 8,900. June 18 was ushered in by a marked erythema at 7:50 A.M. followed in about four hours by wheals with a later temperature rise to 102.8° (rectal), but no chill. The white count had now fallen to 5,400. No malarial plasmodia could be found.

*From the Department of Internal Medicine, Washington University Medical School, and the Jewish Hospital, St. Louis.

Name Mrs. E. S. No. Admitted Room Admitted

Record Respiration Green, Pulse Red, Temperature Black, Leucocytes Purple.

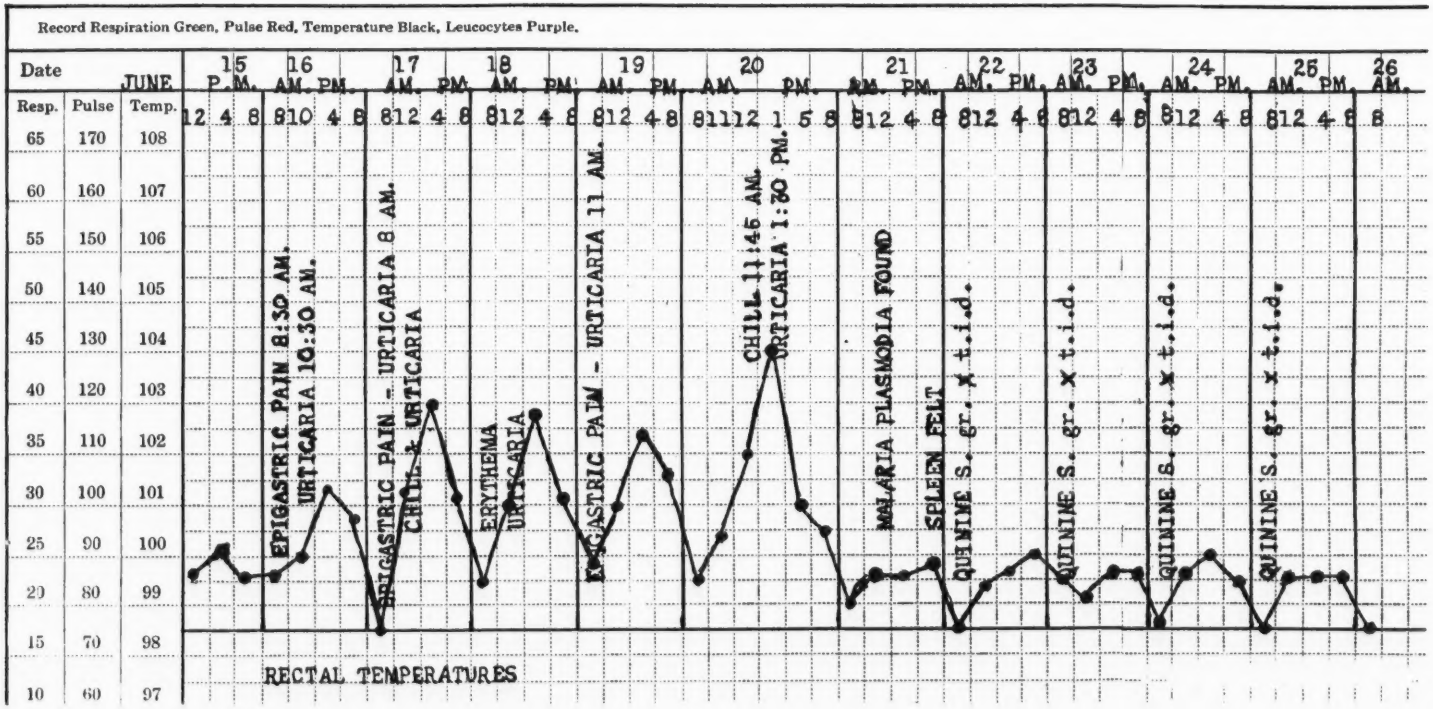
Date
JUNE
15 16 17 18 19 20 21 22 23 24 25 26
P.M. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM. PM. AM.
Resp. Pulse Temp.
65 170 108
60 160 107
55 150 106
50 140 105
45 130 104
40 120 103
35 110 102
30 100 101
25 90 100
20 80 99
15 70 98
10 60 97
EPIGASTRIC PAIN 8:30 AM.
URTICARIA 10:30 AM.
EPIGASTRIC PAIN - URTICARIA 8 AM.
CHILL & URTICARIA
ERYTHEMA
URTICARIA
EPIGASTRIC PAIN - URTICARIA 11 AM.
CHILL 11:45 AM.
URTICARIA 1:30 PM.
MALARIA PLASMODIA FOUND
SPLEEN FELT
QUININE S. gr. X t.i.d.
QUININE S. gr. X t.i.d.
QUININE S. gr. X t.i.d.
QUININE S. gr. X t.i.d.
RECTAL TEMPERATURES

Fig. 1.

The following day a similar reaction occurred, with a white count of 5,300. No organisms were seen. On June 20, during an examination, the patient developed a severe chill and urticaria without itching, pain, or vomiting, but with a temperature of 104° (rectal). The spleen had not been palpated by any one of several observers. The following day, however, the spleen was outlined for the first time, about 1 cm. below the costal margin, and coincidentally abundant malarial plasmodia (double tertian infection) were found in the blood smears. Quinine sulphate in 10-grain doses three times a day was started on June 22, and as shown on the chart there were no further fever, chills, or recurrence of erythema, urticaria, or epigastric pain. Blood culture showed no growth. A gall bladder x-ray series (made June 24 with Tetradol capsules) showed a normal filling and emptying of the gall bladder and no calculi were shown. All other laboratory studies were within normal limits. The patient was discharged from the hospital on June 26. She returned to her home in Tennessee a few days later with directions to continue 10 grains of quinine every night for ten weeks and to take a prophylactic course of quinine every spring. About six weeks later, a letter received from her stated that she had been perfectly well since leaving the hospital.

Urticaria, according to Thayer,[1] is the most common rash in malarial infection, and Mannaberg[2] holds that in this infection, urticaria occurs about as frequently as herpes. Riesman[3] distinguishes the following three types of urticaria in malaria, and reports a case corresponding to the first type: (a) that accompanying the malarial paroxysm, and usually appearing during the febrile stage; (b) that replacing the chill, the other feature of the paroxysm remaining; (c) that taking the place not only of the chill but also of the entire paroxysm.

Engman[4] has stated that the third type is the one most frequently seen by dermatologists, and reports[5] four cases, one of which was complicated by an angioneurotic edema. Garin and Pasquier[6] relate that of 135 malarial patients, over 30 per cent developed recurring urticaria either with or following malarial attacks. Froes[7] reported a case of quartan malaria with neither chill, fever nor sweats; the only manifestation being attacks of urticaria. Deuskar[8] has reported a case similar in nearly all respects to the one herewith described. These, among others, would seem to confirm a definite relationship of urticaria with malarial infection.

There is, in addition, clinical evidence that suggests a relationship of bronchial asthma (generally accepted as a manifestation of allergy) with malaria. Thus Zallocco[9] reported a child of four years who had had intermittent attacks of fever (39° to 40° C.) which began with a chill and ended with a profuse sweat. During these attacks, which lasted several hours, there was respiratory oppression with expiratory dyspnea. This was relieved by epinephrin. Treatment with quinine afforded relief of symptoms. Also, Thonnard-Neumann[10] studied 21 cases in the flat coast district of Haiti. He found that they fell into two groups. In the first group, with a high average age, the asthma recurred year after year at the close of the rainy season, when the hitherto prevailing sea wind gives place to a land wind. Only

about a third of these patients had malaria. In this group, treatment of the malaria had no influence on the asthma. In the second group of patients, the oldest of whom was forty-three years, the asthma was not seasonal in type. In all of these patients, malaria was present and in each case treatment of the malaria cured the asthma.

Since Casoni[11] described the reactions which occur when hydatid cyst fluid is injected intradermally into patients with echinococcus disease, there has been a very considerable study of this phenomenon. Kellaway,[12] Testi,[13] Gasbarrini,[14] Pontano,[15] Luridiana,[16] Serra[17] and Fairley[18] have studied it in reference to echinococcus disease. Botteri[19] has demonstrated that active and passive anaphylaxis may be produced with the cyst fluid; also that a small dose of the fluid would protect against an otherwise fatal dose. Rackemann and Stevens[20] have been able to demonstrate the presence of reagins by means of the passive transfer method of Prausnitz and Kustner[21] in two patients with echinococcus disease.

Fulleborn[22] concludes that a positive skin test to strongyloides extract is specific for infestation with this parasite. Schrople[23] found delayed positive reactions by intradermal testing with an extract of oxyuris vermicularis in cases infected, or previously infected, with oxyuris. Skin tests with extract of ascaris lumbricoides, and studied in relation with ascaris infestation, have been made by Fulleborn,[24] Rackemann and Stevens,[20] Brunner,[25] Coventry and Taliaferro,[26] also by others. At the present time, there is no unanimity of opinion as to the correlation of a positive skin test with the presence of an ascaris infestation. However, Coventry[27] has found that cutaneous reactions, of the delayed type, follow the intracutaneous injection of ascaris extract in rabbits and guinea pigs infected with ascaris; and that this reaction may persist for months after the total disappearance of the worms.

Extracts of Dibothriocephalus latus, Taenia solium (Brunner[25]), trichinae (Fulleborn[24]), trichuris (Coventry and Taliaferro[26]), hookworm (Coventry and Taliaferro[26]), and liver flukes (Kellaway[28]) have likewise been employed for skin testing in an effort to evaluate this as an etiologic diagnostic method.

Parasitic infestations apparently have the ability to induce the allergic state in individuals so affected. Furthermore, parasitic extracts when administered intradermally may also induce allergic responses other than the local reaction. Ransom[29] has studied the effect of swine ascaris fluids on susceptible individuals, and has reported a case where the contact of fresh ascaris fluid with a recent abrasion on the wrist was followed by a local reaction, generalized urticaria, swollen face, edema of the eyelids, breathlessness and a rapid heart rate. Ransom, Harrison and Couch[30] reported an individual who developed asthma on exposure to ascaris. Brunner[25] reported three cases (one of hay fever

and asthma, one of previous trichinosis infection who had occasional wheezing respiration, and one of nonsensitive asthma with a past history of round worm infestation) in which intradermal testing with ascaris, 1:100 solution was followed by a constitutional reaction manifested by bronchospasm. A constitutional reaction is also possible in an apparently nonallergic individual, as noted by Rackemann and Stevens.[20] During a passive transfer experiment with ascaris extract on a normal noninfected man with a negative history for allergy, there occurred large local reactions at both the prepared and unprepared sites, and shortly thereafter restlessness, itching, wheezing, and generalized urticaria were manifested.

In view of the foregoing, it is suggested that an urticaria occurring as the result of infestation with malarial parasites may be fairly held to be an allergic phenomenon.

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OBSERVATIONS ON FATAL BRONCHIAL ASTHMA*

A Report of Two Cases

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THE paucity of postmortem material in cases of bronchial asthma is well known. Rackemann,[1] in a series of one thousand cases observed during a period of six years records five deaths and reports one autopsy. Huber and Koessler,[2] in a comprehensive review, collected fifteen cases and reported six carefully studied cases. Lemierre, Leon-Kindberg, and Levesque,[3] reported one, Dehner[4] two, Steinberg and Figley[5] two, one allergic and another bacterial. Kountz and Alexander[6] reviewed three, Ellis[7] eight cases, most of which had symptoms of asthma but also had numerous complications which led him to conclude that the pathologic anatomy, as revealed in his cases, constituted no exposition of the cause of the disease.

Many cases reported in the older literature such as his, with the syndrome of asthma, naturally represent complicated pictures. Asthma, a term used similarly to rheumatism has long served as a convenient scrap basket for disease processes associated with spasmodic dyspnea. Modern effort at differentiation into allergic and so-called non-sensitive types has perhaps brought us nearer to a better understanding of the morbid anatomy found at postmortem. It has also enabled us to interpret the older pathologic descriptions of fatal cases in the light of this newer knowledge and to assign them into their proper spheres. And yet, in spite of the clear-cut distinctions that we are at times enabled to make clinically, the appearances presented at the autopsy table, obviously end-results of prolonged asthmatic insults, are sufficiently complex to make us raise the question again, as to what criteria we can employ to state definitely that such and such lesions are characteristic of allergic, and others of so-called bacterial asthma. Is the presence of eosinophilia the pathognomonic, histologic criterion of allergic bronchial asthma? If so, how is one to explain the eosinophilic bronchitis without any asthma and those cases of asthma in which during life no positive finding of sensitization had been established while the postmortem microscopic sections reveal the presence of eosinophilia. Obviously there are breaks in the chain of available evidence. We can only reconstruct from information gathered from autopsied cases, such as that reported by Huber and Koessler of an infant of fifteen months, presumably a case of food allergy, and deter-

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mine what may be accepted as a basis for human allergic or nonallergic asthma. Bearing in mind such characteristics, we can readily understand that an asthmatic patient dying at the age of thirty or forty after having had asthma for a number of years, will present a variety of organic changes superimposed upon tissues rendered susceptible by virtue of their allergic state to infection, inflammation, and processes of repair. Naturally such changes are not only confined to structural alteration in the lung parenchyma or bronchi alone. Depending upon the length and extent of tissue injury and the consequent diminution in vital respiratory fields, alterations in the capillary bed and circulatory changes resulting therefrom must follow. *Pari passu* with these

Fig. 1.—Case 1. Anterior view of the extreme bullous emphysema. The light areas represent the bullae on the surface of the lung. In the center is the right ventricle of the heart, the tremendous hypertrophy of which causes it to fill the entire space between the right and left lungs.

there may arise a series of events characterized by hypertension of the lesser circulation, atherosclerosis of pulmonary vessels, and right-sided cardiac insufficiency which may lead the asthmatic to a cardiac death.

CASE 1.—6569. A woman, single, age thirty-five, was admitted March 18, 1922. The family history was negative. In July, 1919, the patient was seized with choking sensation in her throat, which persisted for about twelve hours and recurred three to four times at night. These attacks kept on increasing in severity and were relieved by burning stramonium leaves. In the hope of obtaining relief she underwent a nasal operation, but with no improvement. Climate seemed to have no relation to her attacks. Skin test showed her to have questionable reactions to ragweed and beef.

Four days before admission, that is, March 14, 1922, she had a very severe attack of asthma which kept her awake all night. Following that she became

feverish and developed a severe cough. Fever ranged between 100° and 103°. She also noted that her legs were swollen.

Physical examination showed dullness at the right base, sibilant and sonorous râles. Heart borders were not made out on account of emphysema. The heart sounds were of poor muscular quality and no murmurs were heard. Blood pressure was 140/80.

Blood count was 95 per cent Hb. R.B.C. 4,760,000. W.B.C. 6,100. Polys. 80 per cent. Eosin. 2 per cent. Monos. 2 per cent. Lymph. 19 per cent.

On March 20, 1922, x-ray of her chest was reported as showing a pneumonic process over the right base, with pleural adhesions. Examination of her sputum

Fig. 2.—Case 1. Large bronchus showing contraction and folding of the wall due probably to bronchial spasm. *A*, Dilated mucous glands opening into the lumen of bronchus. Note the characteristic viscid mucus filling the bronchus. *B*, Hypertrophied muscle encircling the distended bronchus.

during this time showed the presence of anhemolytic and hemolytic streptococci, and micrococci catarrhalis. On March 31, her condition gradually subsided. The temperature became normal. The lungs were clear, and no manifestations of asthma were present. The final note made on the chart was bronchopneumonia with complicating asthmatic symptoms. She was discharged on April 3, 1922.

On February 1, 1929, the patient was readmitted to the hospital, complaining of very severe cough, swelling of her legs, and a temperature which was 104.2°. At this time she gave the following history:

About nine years ago, when a Red Cross worker in an army cantonment, she began to experience shortness of breath, wheezing, and dyspnea. This imperceptibly

increased, and about one and a half years later, she observed also a swelling of her ankles on prolonged standing. With the dyspnea now came alarming asthmatic crises at irregular intervals. These subsided within the past four to five years without any reason.

Nasal infection was ruled out. Thorough examination for foci of infection was negative. Skin sensitization tests revealed no applicable etiology. Colonic irrigations and various medication proved ineffective. The dyspnea had no chronologic or climatic cycle, nor was it influenced by any discoverable environmental condition.

The edema, at first at the ankles, began about five years before admission to spread up the lower limbs, involving finally the entire extremity. It had usually a

Fig. 3.—Case 1. High power view of the herniation (*A*) of the bronchial wall brought about by the persistent cough due to chronic bronchitis. This is also evidenced by the loss of ciliated epithelium of the bronchial wall. The lumen (*L*) is filled with mucus, desquamated epithelial cells, leucocytes and some eosinophiles.

pale, faintly cyanotic hue; the scarlet flush of the extremities up to the midthigh was of only two to three days' duration, accompanied by soreness and pain. In addition, weeping ulcers on her legs appeared ten weeks before admission and were exquisitely tender.

The edema of the lower extremities and of the buttocks assumed an enormous degree since July, 1928. Coincidentally a progressive tumescence of the abdomen had been noted.

Approximately a year before admission she began to note progressive diminution of the menstrual flow, punctuated three months later by amenorrhea, which has persisted. In its stead a cycle of molimena—characterized by backache, hypogastric

cramps, and puffiness of the right cheek with flushing, recurring every two weeks, was present. Coincident with these, her symptoms of dyspnea and edema were distinctly aggravated, just as they had been in the past, seven to eight years previously, with the onset of her menstruation. She emphasized the fact that her dyspnea and edema were especially noted with her menses and were fluctuant with them. During the three to four months prior to her last admission her cough, which was profuse and accompanied by whitish tenacious sputum, had decidedly diminished.

Physical Examination.—The patient was acutely dyspneic, orthopneic, and afebrile. Her chest was in a state of inspiration. The expansion was very limited. The

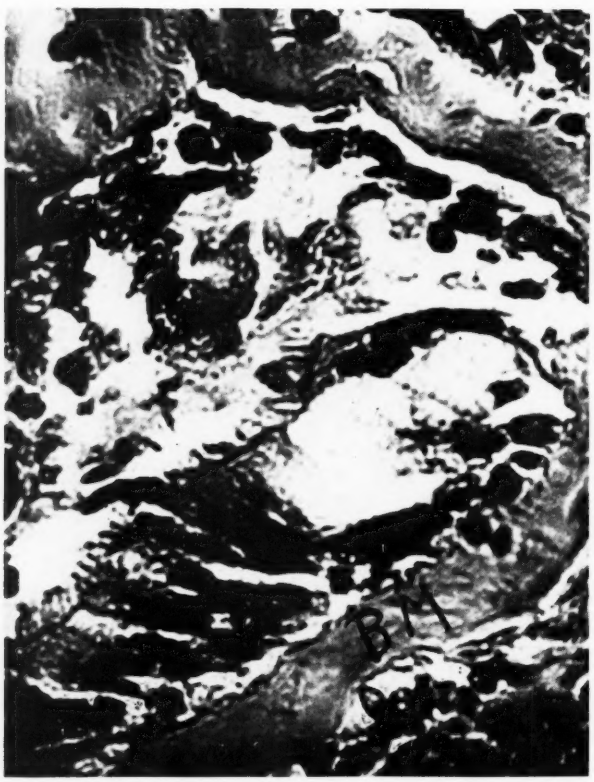

Fig. 4.—Case 1. Mucinous metaplasia of the ciliated epithelium lining the bronchial wall. Note the hyalinization of the subepithelial basement membrane *B. M.* under high magnification.

breath sounds were vesicular, and expiration was prolonged. There were a few high- and low-pitched musical râles.

The heart was transversely enlarged. There was a high-pitched systolic murmur heard at the apex, transmitted toward the sternum. There was also a systolic murmur at the base localized to the second and third interspaces. Gallop rhythm was present.

The abdomen was distended with fluid. The liver was enlarged four fingers below the costal margin. The spleen was not palpable.

The radial arteries showed a moderate amount of sclerosis. The blood pressure was 120/80.

Both extremities were discolored, reddish blue in color and swollen to about twice the normal. Several irregular shallow ulcers were present on each leg. There

was edema of legs and thighs. The course of events was brief. She grew progressively worse and four days later suddenly died.

The blood count on admission was: Hb. 102 per cent. Eosin. 4 per cent. W.B.C. 9,600. Lymph. 16 per cent. Polys. 80 per cent. Mono. 4 per cent.

AUTOPSY FINDINGS

The autopsy reports in this and the second case are confined to those features which have a direct bearing on the problem in hand. Descriptions of the rest of the organs are omitted because of the negative findings.

Body is that of a well-nourished, adult female, thirty-four years of age. There is present marked cyanosis of the lips and fingers and congestion of the conjunctivae. Both lower extremities are edematous.

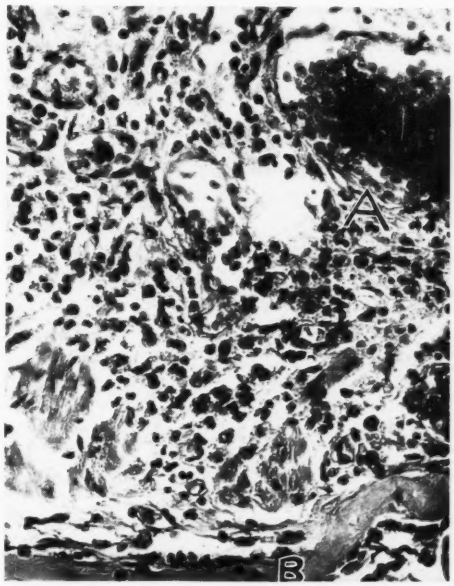

Fig. 5.—Case 1. *A*. Eosinophilic infiltration within the bronchial wall. High magnification. *B*. Hyalinization of the basement membrane.

Chest.—The pleural cavities contain a few c.c. of clear fluid. Both lungs weigh 1225 gm. The left upper lobe is bound down to the chest wall by fresh fibrous adhesions, easily torn through. The right lung is bound down more firmly, especially to the diaphragm and to the upper part of the chest wall. These latter adhesions can only be broken through with some difficulty, tearing the parietal pleura off the chest wall in this process. Both lungs are markedly emphysematous, the right more than the left, showing on its surface marked bullous emphysematous blebs, reaching the size of a small plum. Palpation of the left lung reveals it to be very elastic and crepitant. The cut surface of the upper lobe is dark red, fleshy and hemorrhagic, while the lower lobe reveals a well-aerated and normal appearing surface. The trachea is negative. The bronchi, especially in their smaller branches, show an edematous and inflamed mucosa. The lumen is filled with plugs of viscid mucus.

Heart.—The right ventricle and auricle are tremendously dilated and somewhat hypertrophied, occupying the entire anterior aspect of the heart and overlapping

the left auricle and ventricle. The left ventricle is normal in size. The heart weighs 525 gm. The myocardium is firm and dark red in color. The valves are negative. The aortic orifice is 6¼ cm. in circumference, the pulmonary wall is thicker than normal and in the finer branches are noted many small areas of atherosclerosis. The aorta and coronary arteries are negative.

No abnormalities are found in the rest of the organs.

Pathologic Diagnosis.—Chronic bullous emphysema of both lungs.
Chronic bronchitis.
Atherosclerosis and dilatation of pulmonary artery.
Dilatation and hypertrophy of the right auricle and ventricle.
Chronic passive congestion of liver, kidneys, spleen and intestines.
Ascites.
Anasarca.

Microscopic Examination of the Lungs:

I. Lungs show areas of marked emphysema.

II. Content of Lumen of Bronchi.—Bronchial epithelium is markedly flattened. the ciliated epithelium has disappeared in most areas. It has been replaced by squamous epithelium. About the bronchi there are extensive areas of fibrosis with lymphatic infiltration. The lumen is filled with mucous plugs. In places there is evident herniation of the walls of the bronchi.

(a) Basement membrane is thickened, and has a hyaline appearance.
(b) Subepithelial layer contains many eosinophile cells, moderate number of lymphocytes and polynuclear leucocytes.
(c) Muscle tissue. Marked hypertrophy. Infiltrating the muscle bundles are numerous eosinophile cells, some round cells as well as polymorphonuclear cells.
(d) Mucous glands. Gland duct epithelium contains numerous goblet cells. There is a dilatation of all the mucous glands which are distended with mucin.
(e) Fibrocartilaginous layer contains moderate number of lymphocytes.
(f) Blood vessels. Walls of bronchial arteries show considerable arteriosclerosis. Lumina of many arteries markedly narrowed. Peribronchial, periarterial and septal lymphatics are filled with many lymphocytes.
(g) Alveoli. Interalveolar septa are considerably thickened and infiltrated with mononuclear cells and leucocytes. The alveoli are filled with many "heart failure" cells. In the areas where the alveolar septa are thickened the capillaries are for the most part missing, while in other places these are dilated. Some sections show extensive emphysema with marked thinning of the septal walls.
(h) Lymph glands—hemorrhagic.

COMMENT

The important fact to bear in mind in this case is that there was no definite evidence of protein hypersensitiveness to account for the asthmatic paroxysms. The presence of extensive adhesions of the left, and especially of the right lung; the marked emphysema, bronchitis, dilatation and herniation of the bronchial wall, are strongly indicative

of the presence of infection. This is further substantiated, microscopically, by the presence of infiltration within the bronchial walls, consisting of lymphocytes, polynuclear cells, and plasma cells. The occurrence of eosinophilia within the bronchial wall, while suggesting the question of allergy, if eosinophilia is to be regarded as a *sina qua non* of such a state, cannot be attributed to any discoverable protein susceptibility during life. The striking right-sided hypertrophy and dilatation of the right ventricle and atherosclerosis of the pulmonary arteries, secondary to the severe emphysema was probably responsible for the death of the patient.

CASE 2.—6773. A dress operator, age twenty-three, was admitted to Mount Sinai Hospital on May 10, 1929. There was no family history of allergic diseases. The significant point in her past history was that for many years she had been subject to head colds associated with nasal obstruction.

The present illness began six months before admission, i.e., January, 1929, with sudden severe attacks of dyspnea and pain in the chest. These were relieved by adrenalin and smoking of stramonium leaves, after the expectoration of tenacious mucus. The attacks were aggravated by inhalation of smoke-laden atmosphere and increased in frequency until they occurred four to five times daily and two to three times at night. In the intervals of the attacks she brought up yellowish-green sputum.

Examination and Course.—On physical examination, the important features were as follows:

The patient was extremely cyanotic and orthopneic. The lungs presented marked emphysema, sonorous and sibilant râles. The chest was fixed, and breathing was accompanied by spasm of the muscles of the neck. The heart and abdomen were normal. X-ray of the chest showed no abnormalities. The heart was normal in size and shape.

Examination of the nose and throat revealed an ethmoiditis and moderate edema of the turbinates on both sides. On May 16, 1929, the x-ray of the nasal accessory sinuses showed cloudiness of both antra and of the right and left ethmoid regions. There was also some haziness of the sphenoid. The blood count showed: W.B.C. 6450. Polynuclear cells 51 per cent. Lymphocytes 40 per cent. Eosinophiles 9 per cent.

The skin test showed questionable reactions to rabbit, camel, and cat hair. She did not react to pollens, although the pollen season was on. Apparently the reaction to the inhalants had no applicable etiology, inasmuch as she lived in a hospital room, which was free of any of the inhalants to which she had doubtful reactions. During her stay, the attacks would vary in severity. On May 19, she was given 0.5 c.c. of stock typhoid vaccine, subcutaneously, with no effect on the severe paroxysms to which she was subject. The attacks continued in severity. On June 17, she was given 0.1 c.c. of typhoid vaccine, intravenously. The *status asthmaticus* persisted inseverity; her temperature gradually rose to 107° in spite of all therapeutic measures, and she died in a paroxysm of dyspnea.

AUTOPSY FINDINGS

The body of the patient shows no unusual features.

Chest.—There is no free fluid in the thoracic cavities. There are slight adhesions to the left apex. The left lung weighs 400 gm. It is about normal in size and the pleural surfaces are smooth and shining. No consolidated areas are felt. There are small scars at the apex. The organs crepitate throughout. On

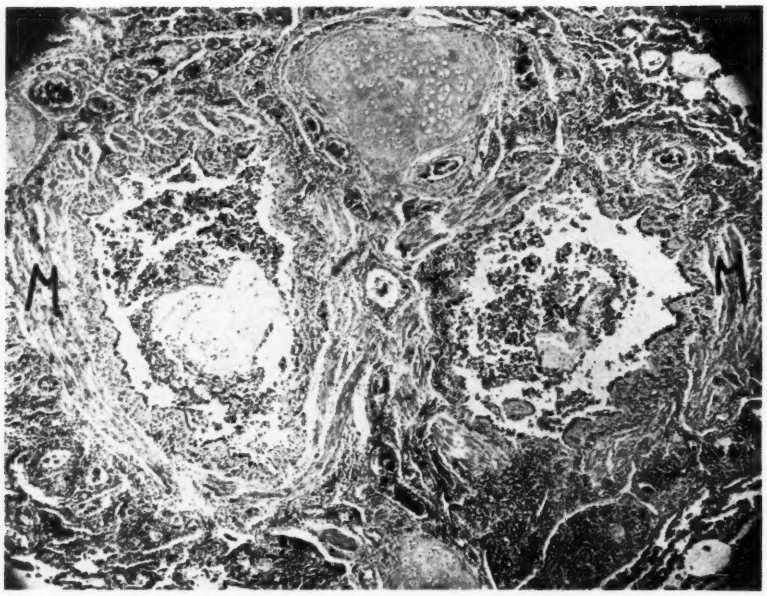

Fig. 6.—Case 2. Two bronchi bifurcating. Note the hypertrophied muscle (*M*) surrounding the bronchi. The contracted lumen is filled with viscid mucus. The subepithelial basement membrane shows hyalinization.

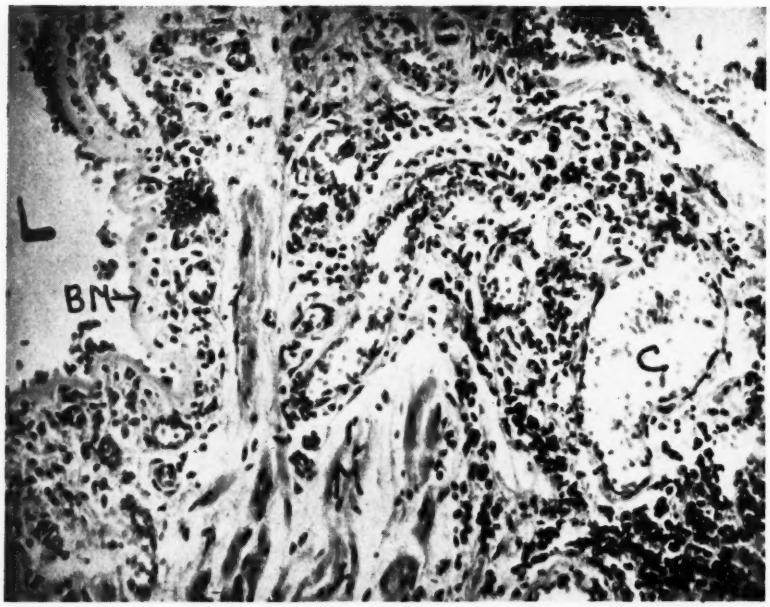

Fig. 7.—Case 2. *A*. Lumen of bronchus, L. Denudation of the mucosa exposing the hyalinized basement membrane, *B. M. B*. Inner layers of the wall of the bronchus consisting of hypertrophied muscle fibers (*M*) and dilated capillaries (*C*) surrounded by eosinophile cells some of which invade the muscle fibers.

section they are slightly hyperemic. The right lung weighs 450 gm. There is a small calcified nodule in the upper part of the lower lobe. Otherwise the organ shows a similar picture to the other lung. The trachea is slightly injected. The bronchi are filled with very thick, bloody mucus throughout the lung. The peripheral bronchi are slightly dilated. This is more marked especially in the lower lobes. The pulmonary arteries are normal.

Heart.—Shows no abnormalities. The rest of the organs present no outstanding pathologic findings of any significance.

Diagnosis.—Chronic bronchitis with dilatation of the bronchi.
Acute passive congestion of the liver, kidney and spleen.
Parenchymatous degeneration of liver and kidneys.
Calcified tuberculosis of the right upper lobe and apex of lung.

Microscopic Examination of the Lungs:

I. Lungs. Moderate emphysema.

II. Bronchi. Dilated, filled with mucus, mononuclear cells, and desquamated epithelium. The ciliated epithelium is replaced by a squamous epithelium.
(a) Basement membrane thickened and hyalinized.
(b) Subepithelial layer is infiltrated with eosinophiles, lymphocytes, polynuclear and plasma cells.
(c) Muscle fibers are hypertrophied and here and there infiltrated by eosinophile cells.
(d) Blood vessels are congested.
(e) Alveoli near the bronchioli are occasionally filled with mucus (probably aspirated agonally). Their capillaries are congested, ruptured in places, filling the alveoli with red cells.

COMMENT

The significant findings in this case are chronic bronchitis and dilatation of the bronchi. There is present a thick, bloody mucus in the lumen of the bronchi and lungs. The heart shows practically no right-sided hypertrophy. Microscopically, there is evidence of cellular infiltration of the bronchial wall, consisting of polynuclear cells, lymphocytes, and plasma cells, indicating that infection was present. The infiltrating eosinophile cells present between the muscle fibers, surrounding also the congested capillaries are similar to those seen in the first case where, as in this one, no evidence of protein hypersensitiveness was to be found *intra vitam*.

DISCUSSION

Correlation of the clinical features in the cases presented with the pathologic findings, forces one to conclude that, from the standpoint of morbid anatomy, there is a close similarity between the two groups, the allergic and the non-sensitive or infectious. Although the precipitating factor in each of these two types is decidedly different—in the allergic sensitiveness to foreign proteins, while in the non-sensitive or infectious, presumably to bacteria—the results of the prolonged action of the irritating agent, as finally seen in the pulmonary tissue, at autopsy seems to be the same in the one as in the other. That the incit-

ing factors exercise their action via the vagus or the parasympathetic system has been shown by Lewis and Auer[8] in animal experimentation. Anatomically there is a striking resemblance in the lungs of the experimental animal and those of the human asthmatic, especially of the allergic variety. If one were to compare the lesions resulting in the protein hypersensitive cases described by Kountz and Alexander,[6] and Huber and Koessler,[2] with those in the infectious cases above described, the following striking similarities would stand out:

Lungs.—Marked or varying grades of emphysema—the bronchi dilated and containing viscid mucus. Bronchial musculature thickened. The epithelium usually desquamated and in places retained, depending upon how much secondary bronchitis is present and the duration thereof. The bronchial basement membrane is thickened and hyalinized in both groups; in our cases it is also invaded by scattered eosinophile cells. The subepithelial layer contains numerous dilated capillaries, surrounded by infiltrations of lymphocytes, leucocytes, and eosinophile cells. In both of our cases eosinophile cells could be seen between the muscle fibers, and in the first case where there was marked atherosclerosis of the pulmonary arteries, eosinophiles were even seen infiltrating the subintimal layer of some of the arterial branches. The muscle bundles were markedly hypertrophied in both groups; the mucous glands in our cases were more enlarged in the first than in the second; in the allergic they also vary, for they may be small in some cases and dilated in others. The fibrocartilaginous layer, while intact in our specimens, has been reported to be ossified in both allergic* and nonallergic lungs. The alveoli in both present dilatation, absorption atelectasis, pneumonic infiltration as well as congestion between the septa. The lymphatic tissue may or may not show any striking change. In view of the similarity in the findings of the two groups, differentiation from a purely pathologic point of view becomes virtually impossible. It would seem from our cases that the lesion induced in non-sensitive asthmatics is so similar to that found in true allergy that one is almost forced to ask whether infection, in the sinuses or lungs of individuals with constitutionally unbalanced vegetative nervous system, does not evoke the same mechanism as in true allergy.

If the occurrence of eosinophilia is a true criterion of the verity of allergic bronchial asthma, then asthma mediated through the presence of infections might be considered a form of allergy to infection. Thus far, however, bacterial allergy as such, has not been proved.

The fact that we are unsuccessful in demonstrating bacterial allergy by means of skin tests may imply either that we have not achieved proper types of antigen or that the bacterial antigen *in vivo* in some way alters the human tissue so that the split products arising there-

*Dr. P. Klemperer, in a personal communication, states that such ossification has been noted frequently in nonasthmatic cases and is of no special significance.

from may in themselves act as sensitizing agents. An analogy so far as skin reactions go, is to be found in the drug idiosyncrasies where no demonstrable cutaneous tests obtain and yet an allergic response consequent upon the absorption of the incriminating drug is unequivocal.

It is worthy of note that while the circulatory phenomena in acute bronchial asthma are presumably transitory physiologic disturbances, associated with the paroxysm, one cannot escape the well-known fact that prolonged and closely recurrent attacks which may be accompanied by chronic bronchitis and emphysema might likewise be associated with permanent changes in the lesser circulation. That the change is apparently not due to asthma alone is substantiated by the findings of Alexander, Luten, and Kountz[9] in a review of fifty cases in which the disease was of ten years' duration or more. These authors record that in their series the heart was "rarely enlarged and often comparatively small." They note that in such cases there is an increased peripheral venous pressure which may rise to 200 to 300 per cent during an attack; a tendency to low blood pressure, and an absence of right-sided preponderance either by x-ray or electrocardiographic studies. In contradistinction to these observations are those of Kahn[10] who by electrocardiographic studies alone reported a right ventricular preponderance in 20 per cent of a series of 50 asthmatics. The inadequate criteria employed in Kahn's studies as to the diagnosis of true bronchial asthma and bronchial asthma associated with other disease processes, renders this observation open to criticism. Huber and Koessler[2] in a review of the literature of necropsies in cases of bronchial asthma, record seven cases and two of their own where the right ventricle was reported dilated and hypertrophied. No precise measurements of the size of the heart were recorded. In our own cases, the first of nine years' duration showed tremendous hypertrophy of the right ventricle, whereas the second case of six months' duration showed practically no change of the right heart. If one therefore takes into consideration the fifty carefully studied cases of Alexander, and others, the cases reported by Huber and Koessler in which only two of theirs showed right-sided enlargement, and two of our own, only one of whom showed this hypertrophy, one must conclude that other factors besides the paroxysmal asthmatic attacks must play a rôle in the hypertrophy.

Examination of the many underlying causes in right-sided cardiac hypertrophy reveals that mechanical influences which permanently interfere with or diminish the bed of the pulmonary circulation are directly responsible for such cardiac change. Among these, chronic emphysema which leads to a diminution of the capillary bed, with resultant increased tension in the lesser circulation is preeminently a factor. In the first case, and those collected from the literature by Huber and Koessler, emphysema and reduction of pulmonary fields due

to chronic pneumonic or pleural disease were the etiologic antecedents of the right-sided hypertrophy and insufficiency. Whether we have to assume a constitutional factor as predisposing to hypertension associated with atherosclerosis of the lesser circulation, leading in turn to the development of right-sided hypertrophy in cases of asthma and emphysema, is a question which requires further investigation.

SUMMARY

1. Two cases of bronchial asthma with fatal termination are reported.

2. Both of these cases were non-sensitive types. Neither the clinical course nor skin tests gave any evidence of the existence of protein hypersensitiveness.

3. The salient pathologic findings were as follows:

(a) Marked emphysema and bronchitis, in the first case. Dilatation of the bronchi leading to herniation of the wall as a result of a persistent cough.

(b) Extensive hypertrophy of the bronchial musculature.

(c) Eosinophilic infiltration of the bronchial wall, surrounding the engorged capillaries and in between muscle fibers similar to the findings in true allergic asthma.

(d) Hyalinization of the basement membrane.

(e) Severe atherosclerosis of the pulmonary arteries, with subintimal infiltration of the wall of some of the larger arteries by eosinophile cells (in the first case).

(f) Marked hypertrophy and dilatation of the right ventricle in the case of nine years' duration. Absence of right-sided cardiac involvement in the case of six months' duration. The hypertrophy of the right ventricle in the first case is due to marked emphysema.

4. The occurrence of eosinophilia as evidence of true allergy and its presence in the non-sensitive cases reported is stressed.

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PYRETHRUM: AN ETIOLOGIC FACTOR IN VASOMOTOR RHINITIS AND ASTHMA*

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THE insecticidal property of the flowers of certain species of pyrethrum, or chrysanthemum, was recognized by the people of Eastern Europe more than a century ago. The facts pertaining to the actual discovery of this property, however, are quite as indefinite as are those connected with its subsequent commercialization in the form of insect powder. Three types of pyrethrum are referred to in this connection, namely, the Pyrethrum cinerariaefolium, Pyrethrum roseum, and Pyrethrum carneum. As early as 1851, Koch[1] made mention of the flowers of Pyrethrum carneum and Pyrethrum roseum in the concoction of Persian insect powder while, among others, Frontali[2] several years later, described the employment of Pyrethrum cinerariaefolium in the manufacture of Dalmatian insect powder. Pyrethrum has now become one of the most popular constituents of insect powders, today representing an extensive industry abroad and in the United States.

HEALTH HAZARDS REPORTED IN THE LITERATURE

With the steady increase in this industry has come a realization of the health hazards to which persons engaged in the gathering of these flowers and their manufacture into insecticidal and disinfectant products are exposed. In the latter connection the work of McCord, Kilker and Minster[3] is of interest. These authors record the occurrence of a dermatitis and accompanying symptoms, of previously unknown origin, among employees of an establishment engaged in the manufacture of insect powders. Investigation established the fact of its prevalence exclusively in departments in which pyrethrum was handled. These cases were all ascribed to one primary condition, a Dermatitis venenata (Pyrethrum dermatitis), admitting of classification into four groups, namely, (1) an erythema venenatum; (2) a vesicular dermatitis; (3) a papular dermatitis; and (4) an anaphylactic type.

About 30 per cent of the 85 men and women employed in the handling of pyrethrum were found to have been affected with the first type of skin lesion. The lesions of these various types occurred at intervals, their appearance and disappearance being governed by exposure to or removal of the source of irritation. Only one example of the anaphylactic type was presented in their series.

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The site and nature of these lesions are described as being identical in each subject during each attack, although more easily induced when the subject perspires freely. This latter circumstance is attributed to an apparent solubility of toxic substances in the perspiration of the workers' bodies. Shortly after entering the dust-laden room the skin of the face reddens, then burns and itches. The cheeks, especially below the eyes, rapidly become swollen, indurated and erysipeloid in appearance. The affected areas become raised and indurated, with fairly well-outlined edges. Following this, the eyes become swollen, the lids at times being closed entirely. Intense pruritus was noted. However, the entire condition disappeared within two days if the individual was removed from the dust irritant. These writers suggest the instiution of trade processes eliminating the necessity of exposure of employees to pyrethrum powder.

Other than the cases just outlined, literature recording the specific effects of pyrethrum on man is meager. The following few reports, however, will serve to illustrate the type of instance published:

C. V. Riley,[4] United States Commissioner of Agriculture, in 1884, records intensifying sleep and stupor as his own personal experience resulting from the fumes of pyrethrum-containing insect powder in a closed room.

A case was described by Boucard[5] in 1858, which tells of bloating of the face, headache, roaring in the ears, symptoms of syncope, pain in the stomach, nausea and sweating, in a woman whose bed had been strewn with insect powder.

Von Wiggers[6] in 1859, abstracting an anonymous publication, reports a restless night, accompanied by bad dreams and intense headache, in a father and son, attributed to Persian insect powder which had been scattered in their beds. A similar experience, also due to sleeping in a bed strewn with insect powder, was reported by Schlagdenhauffen and Reeb[7] in 1890.

Pyrethrum taken by mouth seems also to have caused unpleasant or serious symptoms in a few instances.

WRITER'S SERIES

In addition to the hazards of industrial workers, reported in the literature and in my present series of vasomotor rhinitis and of asthma, which form the basis of the present article, these cases indicate the dangers to which one possessing a specific hypersensitiveness to pyrethrum is exposed throughout the year. An example of the latter type is to be found in Case 2, which was the result of inhaling air laden with the fumes of a popular insecticide. All these cases illustrate, further, that inasmuch as the *plant* pyrethrum (also known as chrysanthemum, feverfew, golden feathers, and pellitory) is encountered in the fields and is cultivated in private gardens, and, commercially, by florists, its

etiologic bearing in cases of vasomotor rhinitis and of asthma must be kept in mind.

All of the patients, in my present series, gave positive skin reactions to extracts of pyrethrum pollen, both by the scratch and intradermal method, and were satisfactorily desensitized.

CASE 1.—Male; aged thirty-five years. For the past five years has had repeated attacks consisting of swelling of the face, eyes, and lips, coming on usually during the summer months, July or August, and continuing until cooler weather, generally about October. There is a moderate amount of sneezing and itching of the eyes coincident with skin manifestations. Family history negative for allergy. Skin tests showed a positive reaction to June grass, ragweed, cocklebur, and a very strong reaction to pyrethrum. Applications of pyrethrum to the skin caused, within twelve hours, an eruption and swelling similar to that occurring during the summer months. This patient comes in daily contact with pyrethrum in his work.

CASE 2.—Female; aged thirty-seven years. Has severe hay fever due to timothy, ragweed and various other pollens. She had not been tested against pyrethrum until she complained of a severe attack of sneezing, itching of the eyes, and difficulty in breathing, occurring after termination of the pollen season. She was then tested against pyrethrum and gave a strongly positive reaction. On questioning, it was learned that the attacks started immediately upon entering her automobile, the interior of which was sprayed with "Flit," a popular insecticide consisting chiefly of pyrethrum.

CASE 3.—Female; aged forty-seven years. For the past ten years has had hay fever, with symptoms beginning in August and continuing until frost. This year, however, has had recurrent attacks of sneezing after termination of the pollen season. This patient gave a positive reaction to ragweed and pyrethrum. She is frequently exposed to pyrethrum, which is cultivated in her own garden.

CASE 4.—Female; aged seven years. This child has had repeated attacks of asthma for the past two months. Positive skin reaction was obtained to horse dandruff, goose feathers, and pyrethrum. The possibility of close contact of the child with insecticides, while playing on the floor or elsewhere, suggests itself.

Pyrethrum belongs to the enormous family of Compositae; it is a section of the genus Chrysanthemum. According to Bailey's Standard Cyclopedia of Horticulture,[8] "the genus Chrysanthemum, as now accepted by botanists, includes many diverse species, so far as general appearance is concerned, nevertheless well agreeing within themselves in systematic marks, by these same marks being separated from related groups. . . . The garden pyrethrums cannot be kept distinct from chrysanthemums by garden characters. The garden conception of pyrethrum is a group of hardy herbaceous plants with mostly single flowers, as opposed to the florists' or autumn chrysanthemums, which reach perfection only under glass, and the familiar annual kinds which are commonly called summer chrysanthemums. When the gardener speaks of pyrethrum, he usually means Pyrethrum roseum. Many of the species described have been called pyrethrums at various times, but they all have the same specific name under the genus Chrysanthemum, except the most important of all garden pyrethrums, viz., Pyrethrum roseum, which is Chrysanthemum coccineum.

"Although the genus is large and widespread, the number of plants of interest to the cultivator is relatively few. Of course, the common garden chrysanthemum, derived apparently from two species, is the most useful. The insect powder known as 'Pyrethrum' is produced from the dried flowers of Chrysanthemum cinerariaefolium and Chrysanthemum coccineum. The former species grow wild in Dalmatia. Dalmatian insect powder is one of the most common insecticides, especially for household pests. Chrysanthemum cinerariaefolium is largely cultivated in California, and the product is known as 'Buhach.' "

Pollination occurs some time between the beginning of June and the middle of July, depending upon climatic conditions and upon the particular species.

In the majority of publications pertaining to insecticides manufactured from pyrethrum, the most efficacious powder is acknowledged to be obtained from the "closed" flowers, namely, those which still contain pollen. The "half-closed" flowers constitute the second grade of insect powder, the most inferior quality being manufactured from the "open" flowers. It would, therefore, seem logical to suppose that the toxic principle is inherent in the pollen. Opinions, however, differ on this point, as will be pointed out later.

THE ACTIVE PRINCIPLE OF PYRETHRUM

The active principle of pyrethrum has been extracted and analyzed by an endless number of investigators, and their varying opinions may be traced almost to the time of the actual discovery of the insecticidal property of this genus of plants. Most of the work has been done in connection with the pyrethrum or Chrysanthemum cinerariaefolium, the species now commonly grown in the state of California and elsewhere in the United States, for the production of insect powder. The diversity of opinion may be judged from the following few conclusions, selected from various reports on the subject.

Schlagdenhauffen and Reeb[7, 9] in 1890, named the active insecticidal principle pyreothrotoxic acid. Sato,[10] a number of years later, found this principle to be embodied in a syrupy resin, which he designated as pyretol. Continuing the investigation of this problem, Fujitani,[11] in 1909, believed the substance to be a neutral ester which he named pyrethron. Reeb, later the same year, verifying the work of Schlagdenhauffen and Reeb in isolating the toxic principle of this insect powder, designated by them, as previously mentioned, pyreothrotoxic acid, stated that it was to be found in a free state in the flowers of pyrethrum.

According to McDonnell, Roark, La Forge and Keenan, whose thorough investigations are of rather recent date, the chemical nature of the active principle seems now to be well understood. It consists, they state, of two closely related complicated esters (pyrethrin I and pyreth-

rin II), present in the flowers to the extent of 0.2 to 0.3 per cent. In addition to these esters, there is present pyrethrum camphor ($C_{10}H_{16}O$), an acrid resin, a volatile oil and an alkaloid (chrysanthemine), etc.

PART OF PLANT HARBORING ESSENTIAL PRINCIPLE

In this connection, the findings of Gerard[12] are of interest. This investigator evidently was the first to be concerned with the exact distribution of the essential principle in the flower. Gerard believed that two active substances are to be found, an oleoresin and a volatile oil, these occurring chiefly around the ovaries and, to a slight extent, in the corolla of the flower.

The conclusions of Yamamoto[13] as to the exact distribution of the active principle, published many years later, are somewhat similar to those of Gerard. Yamamoto found the greatest amount in the ovary of the flower, a small quantity in the sepals, and but a slight trace in the pollen, stigma and petals.

It is evident that none of the writers mentioned regarded the stems or leaves as an important source of the essential principle.

On the whole, it seems a strange and unaccountable circumstance that, although some part or parts of the pyrethrum plant form the essential constituent or constituents of insecticides, the plant itself is reported as being not free from insect enemies. In this connection, a report by C. V. Riley,[14] at that time Secretary of Agriculture, is illustrative. Beetles, he states, devour the blossoms of Pyrethrum cinerariaefolium. Conversely, he tells us, pyrethrum is a most satisfactory substance employed for the destruction of beetles which infest plants, such as pyrethrum.[15]

Regarding observations on the unpleasant effects of pyrethrum when taken by the human being *through the mouth*, a number are cited in *Bulletin 824 of the U. S. Department of Agriculture*. Reports affirming and denying the anthelmintic properties of pyrethrum flowers by Noodt, Schipulinsky, Frontali, and others, are included in the report. The case of an infant of eleven months, who scattered the powder into his eyes, nostrils, and mouth, while playing with a box of insect powder, is reported by Bosredon in 1897. Convulsions and vomiting were induced, heartbeats became feeble, and quickened respiration resulted. All the symptoms, except a slight conjunctival inflammation, however, cleared up as the result of an emetic of ipecacuanha. Ferrand and also Mendelsohn report cases of poisoning with insect powder in human subjects. The only fatal case was reported anonymously, in the *Chemist and Druggist* (1889). A child of two years had eaten approximately one-half ounce of the powder.

In addition to the anthelmintic properties of pyrethrum *flowers*, a few scattered references to their medicinal employment have been found.

A tincture, prepared from the flowers of this plant, is mentioned in the *British Pharmaceutical Codex*[16] as a preventive against insect bites. Insect powder made from the flowers is frequently employed as a dressing for ulcers and wounds, to prevent the formation of maggots, as stated in the *Dispensatory of the United States of America*.

The *root* of the pyrethrum plant, however, seems to be employed, medicinally, more frequently than the flowers.

The dried root of Anacyclus pyrethrum (or pellitory) may be used as a masticatory in certain forms of headache, in rheumatic and in neuralgic affections of the face, toothache, etc., or as a local stimulant, in relaxation of uvula. In the form of pastiles it is also employed to relieve dryness of the mouth.

Notwithstanding the various medicinal uses of pyrethrum, no caution is expressed regarding the risks to which individuals employing it may be exposed.

SUMMARY

Sufficient data have been presented to indicate the divergence of opinion in regard to the various properties of pyrethrum. It is evident that many problems of a definite nature still remain to be solved. A thorough consideration of the literature, therefore, in addition to my own personal experience evidenced by the series of cases herein reported, leads to the following summarization:

It is questionable whether the particular substance (or substances) in which the insecticidal principle or principles is believed to reside is responsible, in whole or in part, for the symptoms of vasomotor rhinitis, asthma, or anaphylactic dermatitis exhibited by some individuals who come in contact with pyrethrum.

It is pointed out by McCord and his coworkers that other substances in pyrethrum having no known insecticidal value are recognized as *local* irritants; that, in addition to the essential principles, pyrethrum camphor ($C_{10}H_{16}O$), pelletorin, essential oils, an alkaloid, inulin, tannin and other factors have also been found to be present. Resinous substances, they state, were found in certain samples of pyrethrum flowers, in as high percentage as 13.76, the yield of alcohol-ether extraction being as much as 30.47 per cent. These resins, oils, camphors, etc., they believe are irritants contributing to the etiology of the skin lesions observed by them.

While the opinion expressed by these writers in connection with *the skin eruption* no doubt applies in some instances, other factors, I believe, may contribute in other subjects. The effect of pyrethrum evidenced by a dermatitis, I agree, may in some nonsensitive individuals be due to a local irritating action; in others, however, it probably is the result of a specific hypersensitiveness.

The more remote manifestations contributing to vasomotor rhinitis and asthma, I believe, may in some persons also be due to irritant re-

actions following actual contact, but they more probably are the result of reactions of a true immunologic nature in an atopic individual who is specifically hypersensitive to the pollen of pyrethrum.

RÉSUMÉ

1. In addition to the hazards encountered by industrial workers in the gathering of pyrethrum flowers and in its manufacture into insect powder, those resulting from the inhalation of fumes from popular insecticides are pointed out in the literature.

2. Attention is directed to another source of danger inherent, not only in the wild variety of pyrethrum, or chrysanthemum, but in the cultivation of the plant in gardens, by private citizens, or in hothouses by florists.

3. Inasmuch as these contacts are presented at all seasons throughout the year, pyrethrum should be regarded as an etiologic factor in perennial rhinitis and asthma, also in certain types of dermatitis.

4. For these reasons the necessity of testing with pyrethrum is emphasized.

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CONSTITUTIONAL REACTIONS IMMEDIATELY AFTER INJECTION OF CONCENTRATED SERUM*

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NEW YORK CITY

IMMEDIATE reactions following the intravenous injection of heterologous serum have been described and the symptoms have been grouped into a well defined syndrome. (1) This communication is a review of the reactions that occurred in some of 371 patients treated at Bellevue Hospital with intravenous injections of concentrated antipneumococcus serum. The therapeutic results and description of the serum have been reported elsewhere. (2) The serum may be described briefly as a solution of the globulins removed from antipneumococcus horse serum by precipitation with water.

The chill and rise in temperature which sometimes follow the introduction of foreign material into the circulation were occasionally encountered in this series of cases but will not be considered in the present discussion. The temporary circulatory embarrassment that sometimes appears in patients with cardiac insufficiency who receive serum is also outside the scope of this article. By immediate reaction we have reference to certain symptoms and signs which follow soon after the administration of serum, such as dyspnea and cyanosis, rapid weak pulse and urticarial skin eruptions, manifestations which are relieved by adrenalin. This is the type of serum reaction named by v. Pirquet and Schick the "immediate reaction."

Twenty-three patients, or 6.1 per cent of 371 treated with intravenous injections of concentrated serum had reactions. In 9 of the patients, or 2.4 per cent, the symptoms were of sufficient severity to alarm both the patient and the physician, and consisted of severe dyspnea and urticaria. In one instance dyspnea alone was present. Seven of the patients had mild reactions which might have been unnoticed except for the fact that patients were usually observed for fifteen minutes after the initial injection of serum. In these 7 patients dyspnea and urticaria were the prominent symptoms. The remaining 6 patients had urticaria, but no dyspnea.

In this study reactions have been observed in respect to:

1. A history of previous sensitization to horse serum or other antigen.
2. The intradermal and ophthalmic test to 1:10 horse serum.

*From the Second Medical (Cornell) Division of Bellevue Hospital.
This study received financial aid from the Influenza Fund of the Metropolitan Life Insurance Company of New York City.

3. The effect of repeated serum injections.

4. The quantity of serum precipitating the reaction and whether the reactions followed the first or a subsequent injection of serum.

Before a patient was given serum he was asked whether he had had asthma, hay fever, hives, or previous injections of serum. Among the 10 patients who had severe reactions there were 3 who had had previous intravenous injections of serum. One other patient with severe symptoms had a definite history of hay fever with spontaneous cure ten years before. Thus only 4 definite histories of possible sensitization to horse serum were disclosed by questioning the 23 patients who had immediate serum reactions. In 19 cases no evidence was found in the history indicating previous protein sensitization.

Because cutaneous and ophthalmic tests have been successful in indicating sensitization states, an intradermal test and an ophthalmic test with nonimmune horse serum (1:10) was performed upon most of the patients about to receive serum. In the intradermal test, the size of the wheal, as well as inflammatory signs such as erythema or edema, were noted at the end of fifteen to thirty minutes. An area of edema one-half inch in diameter with a surrounding erythema was sometimes seen, similar to an urticarial wheal. Irregularity of the edges of the edematous area, or pseudopodia were rare.

Of the 291 patients who were tested intradermally with 1:10 horse serum 17, or 5.8 per cent, were found to have tests one-half inch in diameter. To this group two other patients may be added who had immediate serum reactions and positive local tests of a different type. One had a large hive-like area of local edema about the site of a subcutaneous injection of the concentrated serum. The other patient reacted markedly about a scratch skin-test with 1:10 dilution of normal horse serum.

General reactions occurred in 18 patients who had had tests for skin-sensitiveness. Only 8 of these showed positive skin reactions. The proportion of patients with skin reactions one-half inch in diameter was greater among those who had urticarial reactions (3 out of 4) than among those who had severe dyspnea and greater among the patients with severe dyspnea (4 out of 8) than among those who had only mild dyspnea and urticaria (1 out of 6).

In performing the ophthalmic test 1 or 2 drops of 1:10 horse serum was placed in the patient's conjunctival sac. An injection of the conjunctiva within fifteen to thirty minutes was considered to indicate hypersensitiveness to horse serum. Only one of the 291 patients tested gave a positive ophthalmic reaction to 1:10 horse serum. He also showed a positive intradermal test to a 1:10 dilution of normal horse serum. He reacted locally with a large erythematous and edematous area when 0.2 c.c. of the concentrated serum was injected subcutaneously. No serum was given intravenously to this patient.

Those patients who had severe reactions were prone to have a renewal of symptoms when subsequent injections of serum were given. Intravenous serum administration was continued cautiously in 14 patients after a reaction had occurred. Six of these had repeated reactions while 8 did not. Of the 6 patients who had further reactions 5 were quite dyspneic on the first occasion. Of the 8 patients who did not have recurring reactions, even though serum was subsequently administered, 6 patients had only urticaria or urticaria and mild dyspnea, while only 2 had urticaria and severe dyspnea.

The amount of concentrated serum injected intravenously at one time varied from 1 c.c. to 30 c.c. Reactions followed injection of all the doses within this range. Six patients did not react to the first injection, but did react to subsequent ones.

PATIENTS WITH A HISTORY OF PREVIOUS SERUM TREATMENT

Five of the 371 treated patients had received serum treatment before. On account of the frequent discussion of reactions to injections of serum repeated after an interval, the case reports will be given:

CASE 1.—J. J., a man fifty-four years of age, was admitted on January 6, 1928, to Bellevue Hospital suffering from pneumococcus Type II pneumonia. St. Vincent's Hospital kindly supplied the record that in December, 1919, he had been treated for lobar pneumonia with antipneumococcus horse serum. Two injections of 180 c.c. each were given on December 5 and December 6 of that year without any immediate untoward symptoms. Severe serum sickness with arthritis occurred ten days after serum administration. On admission to Bellevue, on January 6, 1928, nine years after previous injection of serum, the intradermal test with 1:10 horse serum was positive, measuring 5/16 inch in diameter, and the wheal was surrounded by marked erythema. Concentrated serum was administered as follows:

DATE	HOUR	LOT	AMOUNT
1/ 6/28	12:00 Noon	10	5 c.c.
	3:00 P.M.	"	10 c.c.
	5:00 P.M.	"	10 c.c.
1/ 7/28	11:00 A.M.	36	5 c.c.
	4:00 P.M.	38	5 c.c.
	5:00 P.M.	"	5 c.c.
	6:00 P.M.	"	5 c.c.
1/ 8/28	11:00 A.M.	"	5 c.c.
	12:00 Noon	"	10 c.c.
	1:00 P.M.	"	15 c.c.
1/ 9/28	9:00 A.M.	37	5 c.c.
	12:00 Noon	"	10 c.c.
	5:00 P.M.	"	10 c.c.
	9:00 P.M.	"	10 c.c.
1/10/28	12:00 Noon	"	10 c.c.
	5:00 P.M.	"	10 c.c.
	9:00 P.M.	"	10 c.c.
	10:00 P.M.	"	10 c.c.
1/11/28	3:00 A.M.	"	10 c.c.
	12:00 Noon	"	10 c.c.
	5:00 P.M.	"	10 c.c.
	9:00 P.M.	"	10 c.c.

Reactions occurred after every dose. On the first day they were of the following type: A flush gradually appeared on the patient's face and in the course of five to ten minutes deepened into a mild degree of cyanosis. In ten to fifteen minutes an expression of extreme anxiety appeared together with dyspnea and distress over the precordium. Five to ten minims of adrenalin afforded relief at once. No urticaria occurred in this patient. In this respect the reaction differed from all the others encountered. Fifty milligrams of ephedrine seemed to exert a moderating influence upon the attacks. However, after the second day of serum treatment, the reactions were definitely less in severity, and hardly noticeable during the last day of treatment.

CASE 2.—H. M., a man forty-three years of age, was admitted on November 5, 1927, with pneumococcus Type II pneumonia. He had received intramuscularly the same sort of concentrated serum in Bellevue Hospital in November, 1926, one year before. A large amount, 655 c.c. was administered at that time in the course of eight days, all by the intramuscular route, and without reaction either immediate or delayed. He was tested on readmission in November, 1927, by the injection of 0.5 c.c. of the concentrated serum subcutaneously, and reacted with a typical local urticarial wheal. Concentrated serum was administered intravenously one-half hour later as follows:

DATE	HOUR	LOT	AMOUNT
11/5/28	11:30 A.M.	8	1.0 c.c.
	3:00 P.M.	8	0.5 c.c.
	4:30 P.M.	8	1.0 c.c.
	5:00 P.M	8	2.0 c.c.

The rate of injection was 1 c.c. per minute. Two reactions occurred, one after the first, and one after the last injection of serum. They appeared quickly, within one minute after the first injection and within two minutes after the last. The first symptoms were flushing of the face, slight restlessness and coughing. The cough was painful due to acute pleurisy. Noticeable dyspnea appeared in another minute, together with cyanosis, and extreme distress over the precordium. Urticaria appeared in ten to fifteen minutes. The acute distress was relieved by the administration of 15 minims of adrenalin subcutaneously and 5 minims repeated at five minute intervals until a zone of pallor was noted about the mouth. The patient felt prostrated after each reaction for from one to several hours.

CASE 3.—E. G., a man of forty-five, was transferred to the medical wards of Bellevue Hospital from the psychopathic service on February 2, 1927, suffering from pneumococcus Type IV pneumonia. On February 4, he received 10 c.c. of concentrated antipneumococcus serum lot 2. No skin test was done. Five minutes after the injection the patient's face was cyanosed, his dyspnea increased, swelling of the eyelids with itching, lacrimation, and conjunctivitis appeared, and his tongue commenced to swell and cause difficulty in breathing. The swelling of the tongue persisted for twelve hours. He also had a moderate chill. (This lot of serum is one which produced chills in other patients who did not have the type of reaction just described.)

The condition of the patient on admission to the medical wards made it impossible to secure a reliable history. Further investigation brought the information that the patient had been suspected of having diphtheria three weeks before. Willard Parker Hospital reported that on January 15, 1927, he received 20,000 units

of diphtheria antitoxin intravenously without reaction. The diphtheria antitoxin was horse serum concentrated by the method of Banzhaf, and the amounts injected were approximately 20 c.c. intramuscularly and 10 c.c. intravenously. The interval between these injections and the administration of intravenous concentrated antipneumococcus serum was 20 days.

These cases are the only three instances in this series in which intravenous serum treatment was given to patients who had previously received relatively large amounts of therapeutic serum.

Two other patients who had had small intramuscular injections of horse serum were treated intravenously with refined antipneumococcus serum without immediate reactions. The following are the protocols:

CASE 4.—A. McC., a young woman of twenty-one years, had received five 1 c.c. injections of diphtheria toxin-antitoxin, three of them eight months before she contracted Type I lobar pneumonia. Two more 1 c.c. injections were given one week apart just previous to the onset of her pneumonia. Six days after the last toxin-antitoxin injection the skin test was positive to 1:10 horse serum, while the ophthalmic reaction was negative. Concentrated antipneumococcus serum was given in doses of 15 and 20 c.c. without any general reaction. The patient complained of general itching after two of the injections (neither of them the first). Local swelling and redness appeared at the site of the last toxin-antitoxin injection during the three or four days immediately after the administration of antipneumococcus serum.

CASE 5.—H. C., a girl of sixteen, received an unknown amount of scarlet fever antitoxin one year before admission to Bellevue Hospital. Before administration of antipneumococcus serum intravenously, an intradermal test was performed and was positive to 1:100 horse serum. Concentrated antipneumococcus serum was administered intravenously in amounts from 1 to 20 c.c. without any reaction.

Summarizing then the five patients who had had previous injections of horse serum before receiving concentrated antipneumococcus serum, three had immediate reactions, and two did not. The most striking difference between those that had reactions and those that did not have reactions is in respect to the dosage and mode of administration of the original serum. Two of the patients that reacted had had their first injection of serum intravenously while one had had a very large amount intramuscularly. In those who gave no reaction, the previous dose of serum had been intramuscular and of a moderate quantity.

SKIN SENSITIZATION FOLLOWING THE INTRAVENOUS INJECTION OF CONCENTRATED ANTIPNEUMOCOCCUS SERUM

The uniform occurrence of positive skin reactions in the five patients who had had previous injections of serum brought up the question as to whether the patients receiving their first dose of concentrated antipneumococcus serum reacted similarly. The intradermal test and the ophthalmic test with 1:10 horse serum were performed on 25 patients at various intervals during their stay in the hospital, in order to gain

an impression as to what proportion of serum treated patients developed skin sensitivity. Before serum all tests were negative. During the first week after serum administration 9 of 10 tested were still negative. During the second week 4 of 10 tested were negative and 6 were questionable. From the third week on, 14 were tested. Nine were positive, 3 questionable, and 2 persistently negative. None of these patients showed a positive ophthalmic reaction. Thus the majority of treated patients became skin-sensitive to horse serum after three weeks.

DISCUSSION AND SUMMARY

A survey of this group of patients with immediate serum reactions indicates that the reaction was not predicted in any case. Only 4 of 23 patients with immediate symptoms had histories suggesting previous sensitization of any sort. Sensitization to horse serum as indicated by skin tests was not consistently present in patients who had reactions or consistently absent in patients who had no reactions. In spite of the alarming dyspnea of 9 patients none died during a reaction. One death occurred seven hours after a reaction, but this may well have been due to Type I lobar pneumonia, as the patient was suffering from chronic alcoholism and was over fifty years of age. The lack of serious consequences following immediate serum reactions was noted by v. Pirquet and Schick.[1]

These immediate reactions to horse serum should not be confused with the violent response of persons whose sensitiveness to horse protein is of the hereditary type. Such individuals usually have a history of symptoms such as asthma, hay fever, and hives, and show reactions to the ophthalmic test and the skin test performed with horse serum or horse dander. It is in patients of this type that fatal reactions to horse serum occur. The one patient in this series in whom an injection of the conjunctiva was observed after the introduction of 1:10 horse serum may have been of this type. Such individuals are rare, but they may be identified by tests and history.

Skin sensitiveness to 1:10 horse serum does not necessarily mean that the patient will have immediate symptoms following subsequent intravenous administration of refined horse serum. A skin test one-half inch in diameter was present in nearly all patients after they had injections of either the refined or unrefined serum. In two out of four patients who had both previous serum injections and skin reactions one-half inch in diameter no reaction followed administration of serum.

Three of the individuals who had systemic reactions had had a previous injection of a large amount of horse serum, refined in two cases, unrefined in one. The intervals between the first injection and the injections observed in this study were eight years, one year, and twenty

days. A history of this sort in this series of cases indicates the probability of an immediate severe general reaction to intravenous horse serum injections. Two patients who had had intramuscular injections of moderate amounts of horse serum did not have general reactions.

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[2]Cecil, R. L., and Sutliff, W. D.: In press.

400 East 29th St.

A BOTANICAL SURVEY OF MEMPHIS, TENNESSEE, AND SURROUNDING TERRITORY*

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THIS survey covers a period of two years and was made for the purpose of determining the principal trees, grasses and weeds which may be responsible for the production of hay fever and asthma

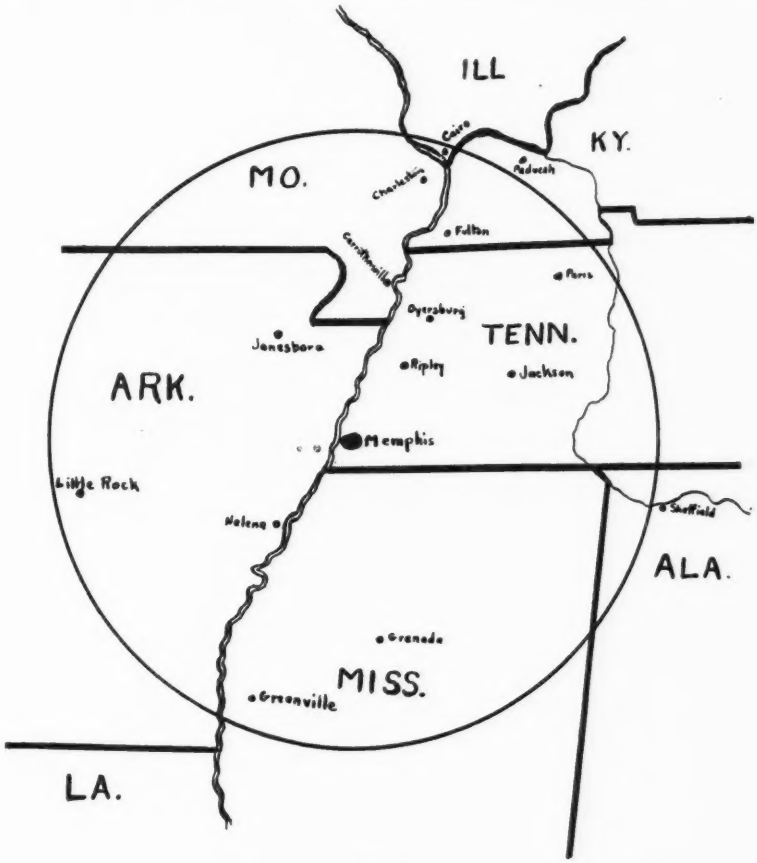

Fig. 1.

in this territory. For this reason only wind-pollinated plants have been studied intensively. Some plants have been encountered which are not included because we believe they are either too few in number or

*Read before the Association for the Study of Allergy, at the Seventh Annual Meeting, Portland, Ore., July 8, 1929.

TABLE I

ANNUAL METEOROLOGIC SUMMARY, 1928, MEMPHIS, TENNESSEE

MONTH	TEMP. (DEGREES FAHR.) MEAN			TEMP. (DEGREES FAHR.) EXTREMES				AVERAGE RELATIVE HUMIDITY (PER CENT)			PRECIPITATION (IN. AND HUNDREDTHS.)				SUNSHINE		WINDS				NUMBER OF DAYS										
	Highest	Lowest	Monthly	Highest	Date	Lowest	Date	7 a. m.	Noon	7 p. m.	Total	Greatest in 24 hours	Date	Total snowfall	Number of hours	Per cent of possible	Average hourly velocity	Prevailing direction	HIGHEST Velocity	HIGHEST Direction	HIGHEST Date	Wind 33 miles per hour or more	Clear	Partly cloudy	Cloudy	Precipitation (.01 inch or more)	Thunderstorms	Dense fog	Snow, trace or more	Highest temperature, 32° and below	Highest temperature, 90° and above	Lowest temperature, 32° and below	Lowest temperature, Zero and below
JANUARY	49	34	42	72	15	4	3	70	55	56	1.65	.62	7–8	0.1	187	60	8.0	SW	45	W	24	2	14	9	8	9	2	1	2	4	0	14	0
FEBRUARY	52	37	45	73	6	19	18	74	60	58	2.42	1.07	6–7	T.	162	51	7.6	SW	31	W	14	0	7	11	11	10	2	1	2	2	0	10	0
MARCH	60	43	52	78	28	29	5	77	64	62	3.14	1.02	15–16	0.2	212	57	7.6	N	32	W	15	0	10	9	12	8	3	0	3	0	0	3	0
APRIL	66	49	57	77	18	35	15	68	54	53	6.70	2.18	5–6	0	235	60	9.0	SW	32	W	13	0	10	7	13	13	5	0	0	0	0	0	0
MAY	78	60	69	86	17	48	8	73	56	53	2.81	0.86	19	0	322	74	6.5	SW	35	W	21	1	15	5	11	6	5	1	0	0	0	0	0
JUNE	82	67	74	89	18	56	6	85	70	71	3.96	1.13	22–23	0	262	60	7.5	SW	38	N	9	3	1	12	17	16	9	0	0	0	0	0	0
JULY	88	73	81	94	4	64	30	82	62	63	1.36	0.73	16–17	0	348	79	5.6	SW	28	SW	22	0	14	13	4	6	7	0	0	0	0	0	0
AUGUST	89	74	81	94	14	61	31	85	68	68	3.91	2.44	30–31	0	305	73	5.6	SW	24	W	30	0	10	14	7	9	10	1	0	0	0	13	0
SEPTEMBER	80	62	71	92	13	46	24	74	54	55	0.06	0.06	1	0	329	88	5.4	NE	19	N	15	0	21	8	1	1	1	0	0	0	0	15	0
OCTOBER	75	58	67	88	10	38	31	82	64	65	5.15	1.74	16–17	0	232	66	5.4	E	24	NW	32	0	17	6	8	9	5	0	0	0	0	2	0
NOVEMBER	59	44	51	80	16	28	26	80	69	67	4.06	1.30	29–30	T.	134	43	6.8	SW	28	SW	21	0	10	7	13	10	0	1	0	0	0	2	0
DECEMBER	52	37	45	70	28	23	8	72	61	62	4.13	1.74	16–17	0	186	61	6.9	SW	25	NW	17	0	18	5	8	7	0	0	0	0	0	9	0
YEAR	69	53	61	94	Aug 14	4	Jan 3	77	61	61	39.05	2.44	Aug. 30–31	0.3	2912	64	6.8	SW	45	W	Jan 24	6	147	106	113	104	49	5	8	5	30	38	0

do not produce sufficient pollen to be considered factors of importance. For example, Scheppegrell[1] mentions sixty-five varieties of oaks that are sufficiently common in the United States to be considered. For our territory, however, only the three varieties of oaks shown are deemed sufficiently abundant to warrant mention although there are other varieties, such as black oak (Quercus velutina) and swamp oak

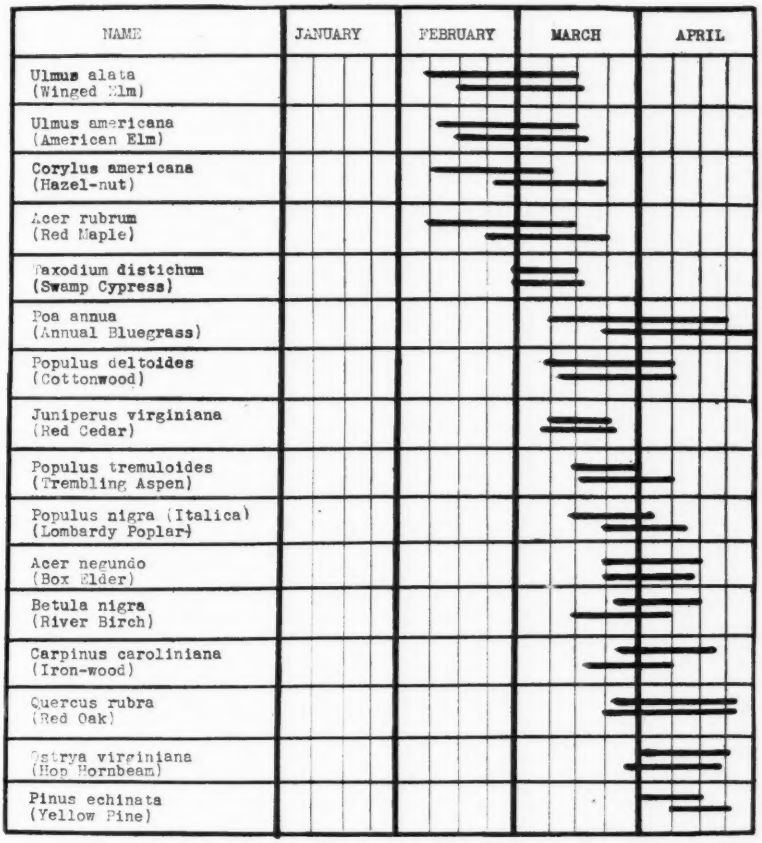

Chart 1.—Upper line—duration of pollination in 1928.
Lower line—duration of pollination in 1929.

(Quercus palustris). The same applies to a few grasses and weeds. As a matter of fact, not all the plants listed in this survey are considered important factors. At times other plants, the pollen of which is practically always insect-borne, have been found to be etiologic factors due to handling or coming in close contact with them. In Chart I the first or top line indicates the pollinating season of each plant for 1928. The second or bottom line indicates the 1929 season. These

lines represent the principal period of pollination. Some plants, such as Bermuda grass and Johnson grass, if kept clipped during the usual season of pollination, will flower later. We have observed these plants in flower late in the fall.

In a survey of this kind it is also of interest to know something of the general topography and weather conditions of the territory under

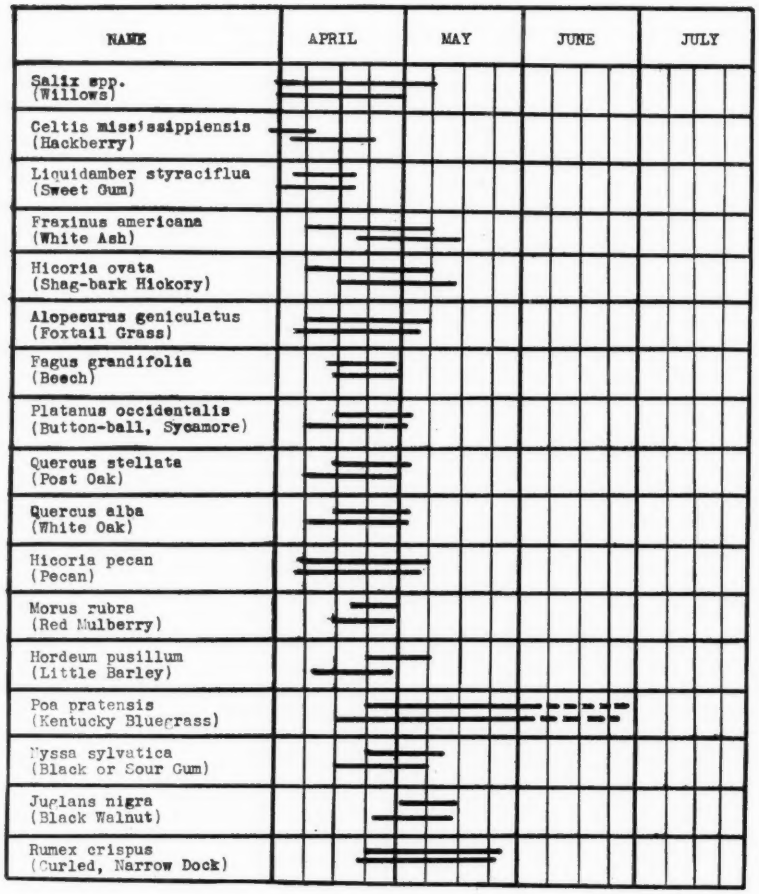

Chart I. (Cont'd).

consideration, since the season of pollination will vary in the same locality from year to year due to difference in temperature, rainfall, and other climatic conditions.

Memphis is located on the east bank of the Mississippi River. As can be seen from the map, portions of five states are within a radius of two hundred miles. This is the area which has been surveyed be-

cause the majority of our patients live within this district (Fig. 1). The altitude of Memphis above sea level varies between 117 and 397 feet. This is higher than the immediate surrounding country. The land across the river in the east portion of Arkansas and that to the south along the river is quite low and is known as the Mississippi Delta. The soil is quite fertile and contains a rich silt loam.

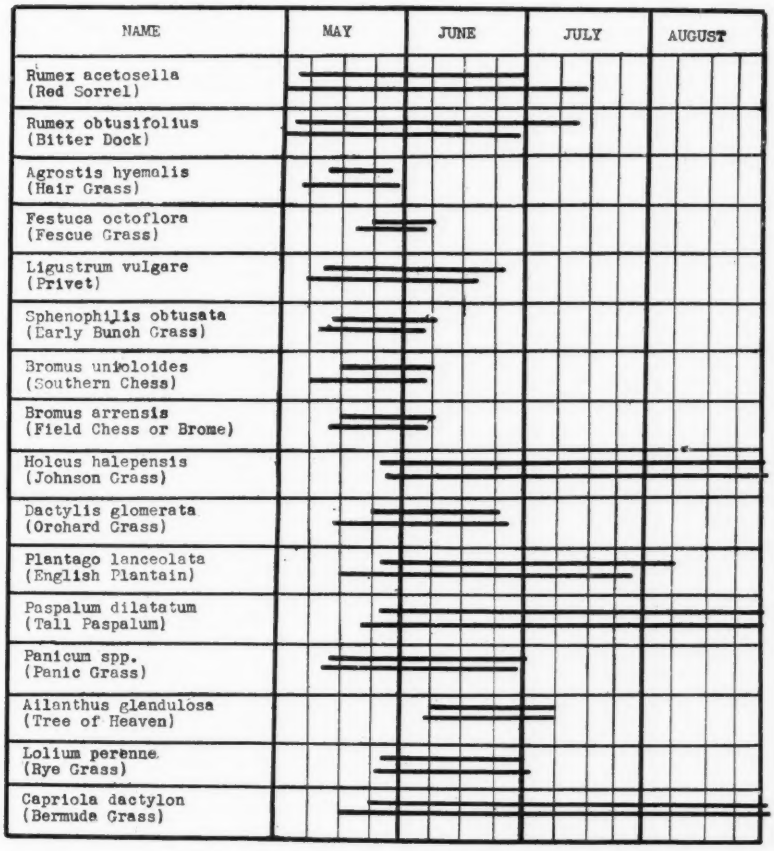

Chart I. (Cont'd).

The annual meteorologic summary for the year 1928 (Table I) shows that the average mean temperature was 61.3°. This was 0.3° below the average normal. The total precipitation was 39.05 inches which was more than 8 inches below normal. The percentage of possible sunshine was 64. Prevailing wind direction was southwest. The last killing frost in spring occurred on March 18, and the first in autumn on November 20.

COMMENT

Hay fever and asthma due to wind-borne pollen is more or less proportional to the distribution and abundance of the plant or plants to which an individual is sensitive and the amount of pollen produced. For this reason the ragweeds (Ambrosia trifida and elatior) are the chief offenders in this territory. At times, however, almost any plant,

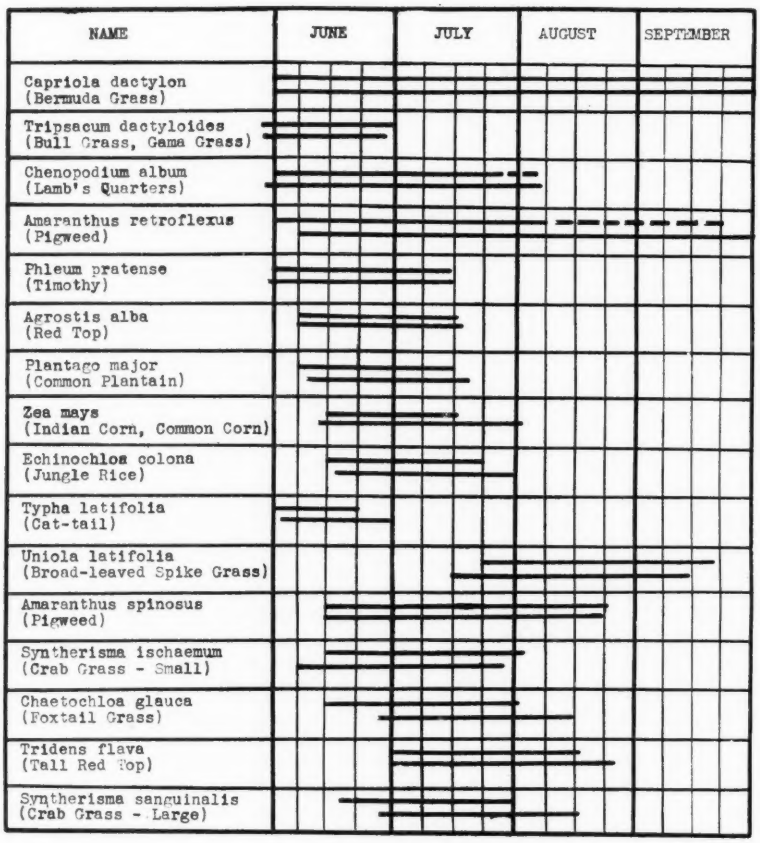

Chart 1. (Cont'd).

although not widely distributed or abundant, may be a principal factor due to close contact. We believe this is particularly so in the case of trees and certain grasses.

We hope the information obtained will serve to acquaint those who have a general knowledge of the flora of the United States with more detailed information concerning this particular locality. For those who have little or no knowledge of the principal wind-pollinated plants in this territory, it should serve as a very useful guide in the treatment

of hay fever and asthma. For instance, mountain cedar (Sabina or Juniperus sabinoides) which causes much hay fever in Texas, and Russian thistle (Salsola pestifer) which is a principal factor in other ter-

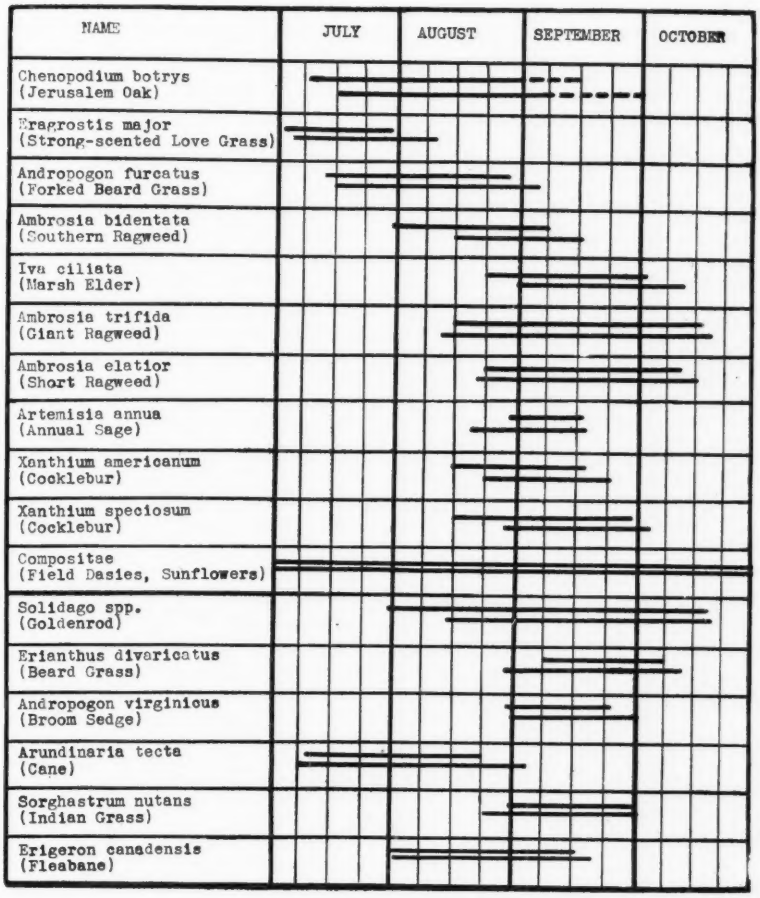

Chart 1. (Cont'd).

ritories are not found in our survey at all. On the other hand, we have plants such as the ragweeds which are not common in areas such as California or the Pacific Northwest.

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1. Scheppegrell: Hay Fever and Asthma, p. 55, Lea & Febiger, 1922.

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ALLERGIC PURPURA

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PURPURA, in general, may be divided into two groups: In one, there is marked diminution in the number of blood platelets with coincident interference with blood clotting; in the other, these changes do not appear. In this latter group, purpura is a symptomatic manifestation of many otherwise unrelated clinical syndromes. Among these, is Henoch's purpura, of which a case report is given. There is marked presumptive evidence that allergy was the underlying cause of symptoms in this patient.

Osler[1] was the first to suggest that purpura together with an erythematous group of skin lesions associated with visceral and joint manifestations (Henoch's purpura), might be due to allergy. However, little was done to determine the soundness of this theory until recently, when Alexander and Eyermann[2, 3] presented several cases of purpura in which allergy was demonstrated to be the etiologic factor.

Henoch's purpura has a varied symptomatology. In the conventional cases, there is severe abdominal cramping associated with purpura of the skin and mucous membranes. On the other hand, arthritic, rather than abdominal symptoms may dominate the picture. The following brief case report illustrates the association of Henoch's purpura and allergy.

The patient was a farmer girl, white, aged twenty-two, single, and of healthy parentage. Her past history was essentially negative, and no allergic manifestations could be elicited. The only family history obtainable was that of one sister who had had eczema. The onset of the present illness occurred in January, 1929, with three attacks of rather pronounced epistaxis, for which no cause could be found at the time. There were no other symptoms, until three weeks later, when aching in the joints and muscles developed with a general draggy feeling. These would last two or three days, then disappear, only to recur in four or five days. This continued until about the first of March, with little change except a slight loss of weight, when moderately severe abdominal cramping, unattended by nausea, vomiting or diarrhea, began. These attacks of abdominal pain would last from a few minutes to an hour or two. They would more often accompany the joint and muscular pains than not. About April 18, during one of the abdominal attacks, large purpuric spots occurred on the lower limbs. These have since been continuous, with new areas appearing every three or four days. By this time, the pain in muscles and joints was fairly constant, and the abdominal pain more frequent but not so severe. No epistaxis occurred since the first three weeks in January. Menstruation was normal during the course of this illness. No blood in stool was noticed. There was no evident rise in temperature.

On physical examination, the patient was found to be well developed. The only

pathologic findings were, medium-sized cryptic tonsils, which were slightly hyperemic; large purpuric spots on lower limbs.

Laboratory findings of the blood, which was examined in detail, were normal. The urinalysis was negative. Skin tests for sensitization were made by the scratch method, and marked reactions to tomato, beef, wheat, and egg yolk were obtained.

The patient was advised to abstain from these foods, and within three days, she felt markedly improved. All symptoms, excepting the purpuric areas which required time for absorption, had disappeared. About two weeks later, she ate a medium-sized dish of homemade ice cream, containing egg. Purpuric spots and some abdominal cramping were noticed the next day, and the patient was more careful about her diet thereafter.

Deliberate feedings of the various foods, to which she was sensitive, gave the following results:

Beef:	No symptoms produced.
Tomato:	No symptoms produced.
Wheat:	Purpuric spots and muscle and joint pains, lassitude.
Egg yolk:	Purpuric spots and abdominal pain.

The patient, by abstaining from wheat and egg yolk, has remained entirely free from all symptoms for a period of approximately six weeks.

Though cases are few, they are suggestive that Henoch's purpura and related syndromes are of allergic origin, and this article is intended, primarily, to present another case of purpura definitely due to the allergic phenomenon.

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The Olney Sanitarium.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

SEVENTH ANNUAL MEETING, PORTLAND, OREGON, JULY 8, 1929

Abstracts of Proceedings

Gastrointestinal Food Allergy. A Study Based on One Hundred Cases.* ALBERT H. ROWE, OAKLAND, CALIFORNIA.

Attention is called to the fact that gastrointestinal symptoms are due to food allergy more frequently than is appreciated by the medical profession, and it becomes necessary for such allergy to be taken into account in the study of all patients with gastrointestinal complaints. Undoubtedly mild allergies to many different foods exist which are difficult of recognition and produce slight abdominal symptoms, especially in patients with other allergic conditions in their personal or family histories.

A statistical study of one hundred cases of gastrointestinal food allergy is presented. The series includes no infants or children in whom the occurrence of gastrointestinal allergy has long been recognized and results in urticaria, eczema, asthma and gastrointestinal symptoms. Such food allergy often persists in adult life and produces lesions of the skin, and of the upper and lower respiratory and gastrointestinal tracts as well as migraine and other less frequent manifestations.

These 100 cases were analyzed as follows:

Males	31%
Females	69%
Family history of allergy	65%
Personal history of	
Asthma	13%
Hay fever	20%
Skin manifestations	32%
Migraine	36%
Food disagreement	77%
Positive skin reactions	
To foods alone	22%
To foods with other reactions	33%
Animal emanations	9%
Dusts	9%
Pollens	10%
Orris root	1%

A more detailed analysis of the symptoms and laboratory findings of 50 cases of gastrointestinal allergy in whom good therapeutic results were obtained is tabulated as follows:

*The complete article will appear in the author's reprint.

Gastrointestinal Symptoms—

Canker sores	20%
Coated tongue	18%
Heavy breath	14%
Distention	32%
Belching	26%
Sour stomach	18%
Epigastric heaviness	28%
Burning-pyrosis	14%
Nausea	40%
Vomiting	30%
Intestinal cramping	24%
Mucous colitis	14%
Diarrhea	12%
Constipation	32%
Proctitis	2%
Puritus ani	4%
Pain and soreness in epigastrium	20%
Upper right quadrant	14%
Midabdomen	16%
Lower abdomen	20%
Ulcer type of pain	10%

General Symptoms—

Weakness	20%
Fatigue	24%
Irritability	10%
Nervousness	12%
Mental dullness and confusion	16%
General aching	6%
Fever	2%

Roentgen Ray of G. I. Tract—

Normal	23 cases
Moderate duodenal stasis	2 cases
Spastic colon	7 cases

Stomach Analysis—

Normal	23 cases
Hypochlorhydria	4 cases
Achylia	3 cases
Former abdominal operations	12 cases
Duration of symptoms	4 mo.-50 yr.
Average	14 yr.
Duration of relief	1 yr.
Excellent results	66%
Good results	34%

These cases were all studied in detail and over 50 per cent had roentgen-ray studies of the gastrointestinal tract.

Each of the gastrointestinal symptoms listed in the above table was taken up in order and exemplified by case reports of which there are forty-four in all. These reports link the presenting symptoms with food allergy and show that withdrawing of the offending foodstuff resulted in relief. In many cases the symptoms of organic disturbances such as peptic ulcer and cholecystitis were simulated.

Emphasis is laid on "allergic toxemia" which results from long-standing food allergy and which is characterized by fatigue, nervousness, mental confusion, and aching of the body as well as such evidences of food sensitization as migraine and gastrointestinal disturbances.

Although no organic lesion was found in any of the cases that were examined roentgenologically, it is noteworthy that 24 per cent of the cases had had abdominal operations because of their symptoms. The average duration of these symptoms before allergic treatment was fourteen years (varying from four months to fifty years). The average relief from elimination diets was one year.

The origin of gastrointestinal allergy is discussed. The symptoms are attributed to a localization of the allergic manifestation in various parts of the digestive tract. Inheritance, overfeeding and associated gastrointestinal upsets are considered the most important contributing factors.

The treatment is based primarily on the elimination of the particular offending food allergen. This occasionally may be discovered by positive skin reaction, but more reliance is placed on elimination diets which the author has worked out. These are instituted after a careful study of the patient's dietary. These diets are appended to the paper.

Each has been devised with the idea of maintaining proper vitamin, salt and caloric intake. The supplementary use of peptone, calcium, and other nonspecific therapy has not proved to be of much benefit. Likewise desensitization by feeding was not found to be a satisfactory procedure. By depending on elimination diets alone, the results were very satisfactory.

An extensive bibliography on food allergy is given.

DISCUSSION

DR. A. T. BLACHLY, PORTLAND, OREGON.—I should like to ask whether you have found any patients in whom foods they liked very much would still produce allergic symptoms.

DR. WARREN T. VAUGHAN, RICHMOND, VA.—My interest in abdominal allergy is centered around colitis more than many of the other conditions which Dr. Rowe has mentioned. I am sure when I go home I am going to widen my interest.

It is very interesting to go over the literature on colitis. There is usually a very short paragraph on the superficial resemblances between spastic colitis, mucous colitis, and asthma. When it comes to therapy the point may be missed altogether for the similarity is not carried far enough.

Hurst in his excellent book on diseases of the colon and constipation, carries this further than any other one man I know of. He devotes several pages to the pathologic similarity and the similarity in the functional pathology between spastic and mucous colitis and asthma, and yet he does not carry this similarity on into therapy. He does, apparently unintentionally, get onto the allergist's point of view in therapy in one paragraph in which he says that a very simple diet must sometimes be started with, such as a plain milk régime with simple foods added from time to time. In other words, he has undertaken the elimination diet.

DR. ORVILLE H. BROWN, PHOENIX, ARIZ.—I have not had as broad an experience as Dr. Rowe, but I believe that I can confirm practically everything he has said. I should like to mention two or three cases very briefly.

A young woman came in to see me complaining of nausea, which she had had for a good many months. She said that it came from milk and milk products, and to emphasize the point that small amounts would oftentimes produce the symptoms, she said that her family would sometimes prepare her food with a little butter without her knowing it, and in a very few moments after eating she knew that some milk product had been combined with the food. Her skin reaction to milk was severe.

At the San Francisco meeting of this Society I reported a method practically the same as that used by Dr. Rowe. He calls his "elimination," and I called mine "food addition," emphasizing that you give practically nothing to start with and then add one food at a time until you analyze the reactions to different foods. I think that is an extremely important method.

Dr. Glenn in Los Angeles gave me a new pointer the other day. He takes a large sheet of paper and has his patients put down, meal by meal, each food eaten and in a column following each meal the symptoms or reactions which may or may not have come from the particular foods eaten. By analyzing those he is able to pick out the worst reactors.

As I have emphasized in previous papers, most commonly it is the food which the patient likes best or of which he eats the most that causes his reactions. That is a point to be remembered. Often it is sufficient to tell a patient to eat what he doesn't like and not to eat what he does like, to rid him of his symptoms.

Dr. Glenn gave me another point which I already had had in my subconscious mind. The food which the patient has when he is seriously ill or which he has eaten when he has not been in the best physical condition is one to which he is apt to become sensitized. He spoke of one case that was sensitized to egg. In going back into the history he found the patient had had a long serious illness and had been given albumin water, which was about the only thing she was able to take. The frequent contact of egg with the diseased gastrointestinal tract caused the sensitization.

Patients may complain seriously of gastrointestinal symptoms which may have gone on for years and yet be relieved after the elimination of one or two foods.

DR. GEORGE PINESS, LOS ANGELES.—I quite agree with the essayist that any tissue may be sensitized. However, in about 1927 Dr. Vaughan and I were in Washington together and we both independently came to one definite theory. I believe he used the term "balanced state"; and I use the term "threshold" or "tolerance point." We both got together on this thing one night. Personally, I believe, and I think Dr. Vaughan bears me out, and also other workers, that each allergic individual has a definite tolerance or threshold or a balanced allergic state. A person who is sensitive to foods and has this state that I mention does not always have his allergy immediately following or within twenty-four hours after the ingestion of this food. If that were true, then why would the food-sensitive youngster give a history of having had an attack of asthma every morning and then as he grew older and his tolerance was lower or some acute infectious disease occurred which broke down his tolerance entirely, have an attack every day, every week, or whenever he came in contact with the substance?

We have another group of cases that are definitely seasonal, and during the rest of the year they have no trouble with food.

I cannot agree with either Dr. Brown or Dr. Rowe that elimination diets are the solution to this problem. In the first place, we are not so sure, as I said before, that the immediate ingestion of that food is going to cause symptoms. Perhaps it may. It may not, depending upon the sensitiveness of that individual.

Another thing of which we are not so sure is the fact that these elimination diets are not elimination diets. There is no man who can sit down and figure out one of the twelve, two of the twelve, six of the twelve, or I do not care how many things in that diet that are possibly causing these symptoms, whether it be an asthma, a gastrointestinal allergy, or any other type.

The elimination diet, in my opinion, that is a choice one is perhaps that of Dr. Brown, which is an addition diet. Incidentally, Dr. Frank McCoy, our famous chiropractor in Los Angeles, has practiced elimination diets and has made himself famous by them. They are nothing new. He has put patients on orange juice and has added other things to that and has acquired a great following.

The point is, I believe, that if an individual is sensitive; if he is an allergic individual and you do test him with a protein, you are going to get reactions. Treating people on the assumption that they are allergic because they dislike certain things I do not believe is a rational method. I believe, with Dr. Rowe, that it is wise to take people off certain foods that they dislike. I believe Dr. Rowe quoted that children who dislike foods should not be forced to eat them. I think that came originally from me. I have found that to be absolutely true in a great majority of cases. Children will not eat the foods to which they are sensitive.

I cannot see where a list of elimination diets is going to give you the information as to the specific sensitivity of the individual. I believe if you test your patients and retest them and then want to give them an elimination diet you should start with one thing and keep on it long enough to find out whether they react. Give it in massive doses so that if they are sensitive they will have reactions from

it. Then add to it until you find they are taking a well-balanced diet in calories and metabolic requirement.

The youngster who is sensitive to foods is going to give reactions some time or other. He travels in a cycle. It is the same with adults. If they do not react the first time they may react at a later time, if you retest and retest.

Dr. Rowe's cases are really spectacular, and no doubt by hard work and constant observation he has been able to prove that these individuals were allergic, but the chief point I want to bring out and leave with you is that every one who is relieved by the elimination of certain foods is not an allergic individual.

DR. ALEXANDER STERLING, PHILADELPHIA.—I think Dr. Rowe deserves a great deal of credit. It is a very difficult clinical test to prove allergy in this particular disease, especially if you want to call anything allergy even though you cannot get any potential reactions upon testing.

In a paper published by me in the *New York Medical Journal* this year I touched upon similar topics. I brought out one point with reference to milk given to individuals who have hay fever and hay fever asthma in the summer and fall season. I have met certain types of patients who were very ill while suffering from hay fever and pollen asthma after the season or in the midwinter. One would think they were almost desensitized and should do well. I could not make out the cause until I ran across an article in the *Pennsylvania Medical Journal*, where cases of gastrointestinal intoxications were described. These appeared to be due to milk from cows that were being fed upon certain grasses. When the cows were put on a different diet, the milk did not make the children ill. It would be interesting to know whether any one else has had the same experience with patients suffering from hay fever or seasonal asthma when partaking of milk products from cows that have been feeding excessively on seasonal grasses.

I had an interesting case of a druggist's wife who had been suffering for fifteen years with gastrointestinal trouble which was diagnosed as ulcer. She was put on a diet of milk and cream but became worse. She called at our clinic to be tested. We found that she gave a plus three reaction to milk. We took her off the milk diet and in six months she was well and has remained well for the past five years.

Personally, I find difficulty with this elimination diet. I should like to know how long a period it takes to determine, by elimination, whether a patient is really ill from the foods one suspects.

DR. ROWE.—For a number of years I tried to demonstrate food sensitization with skin tests alone. My results were, I should say, at least 50 per cent less satisfactory than they have been since I have taken the attitude toward food allergy and the ability to demonstrate positive skin reactions that I have in my elimination diets. I think most of the allergists, especially Alexander and also Eyermann, agree that it is difficult in many instances to show positive skin reactions to food. This realization has been particularly helpful in the asthma of children. I used to have difficulty in demonstrating the allergic cause in some of these cases, but since I have used the elimination diets, certain little children who have had these symptoms for years without help have been definitely relieved.

In regard to the elimination diets that I have proposed, it is necessary to have some system of dieting to follow. Just to say that you can eliminate certain foods may be all right for the men who are definitely interested in allergy and know the problem. We are not, however, the only ones treating these allergic cases. When I published these diets a year ago (and I have been using them now for two years) it was with the idea of recommending something that could be used by the average medical man. During the last year I have been confining myself to the use

of these set diets, with possibly slight changes instead of building a specific elimination diet for individual patients as they have come to me.

I can assure you that I would not have been able to report the cases I have in this article (and I have just reported a few of the most interesting ones) unless I had depended partly on elimination diets and not entirely on skin reactions for the demonstration of food allergy.

The sum total of relief that we have been able to give on the basis of this attitude toward diet has been large. It is possible that I might have been able to show some more skin reactions with retesting but as I have stated before just because you get a skin reaction does not mean that the patient is clinically sensitive to the reacting food. We have seen many patients with positive pollen reactions who are not clinically sensitive. In order to test out the clinical sensitivity, you certainly have to use a trial diet method. We know definitely, in spite of what Dr. Piness says, that the most common foods cause sensitization.

I agree with Dr. Brown that there are many individuals who particularly like the food to which they are sensitive.

Regarding Dr. Sterling's question, I usually see some definite evidence of relief within one or two weeks. If such occurs within a week or ten days I feel that it is worth while to go on with the diets.

DR. ORVILLE H. BROWN.—What are your diets?

DR. ALBERT H. ROWE.—They have been published in the *Journal of the A. M. A.*, November, 1928, and in *California and Western Medicine*, November, 1928, and in *Western Dietitian* for March and April, 1929.

An Unusual Opportunity to Make an Allergic Study of an Entire Community with the Etiology and Results of Treatment. GEORGE PINESS, LOS ANGELES. (For original article, see page 117.)

DISCUSSION

DR. RAY M. BALYEAT, OKLAHOMA CITY.—Dr. Piness is certainly to be congratulated inasmuch as this has involved an enormous amount of hard work and he has some facts well worth while. I merely wish to ask him a question. In figuring his percentage on his family history, I am wondering whether he took into consideration other conditions than asthma and hay fever.

DR. PINESS.—I might say the patients were not questioned by questionnaire. We interviewed every individual in both of those communities, which took a long period of time.

DR. BALYEAT.—His figures, of course, are lower than most of the figures that are shown. Another reason I think they may be low is that the class of people who live there probably would not know about their family tree like most private cases we see. I am inclined to think that if we can really get figures on our family histories, it will approach pretty close to one hundred per cent. Of course, Dr. Piness shows a great many people who have no family history and who never had hay fever until they moved to that community. There is no question but that is true. All of us have seen millers who are constantly thrown in contact with wheat and who become sensitive to wheat. It is common for a rancher who is constantly thrown in contact with cattle to become sensitive to cattle hair. The only question I had in mind was concerning the other allergic conditions.

DR. ALEXANDER STERLING, PHILADELPHIA.—This is really one of the most remarkable pieces of work I could ever dream of: having communities to study on

such a large scale. I suppose none of us could really figure out the number of years it takes for such a study. I understand Dr. Piness said it took three years to accomplish this work. I was surprised at the high percentage of failures he had in those cases. I think it is because he has been giving them injections only every five days and limiting them to twenty injections. Personally I do not stop at giving patients injections every day for two months, and I carry them up to the highest dose to as much as practically ten times the usual dose which causes symptoms.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—I have had an interesting experience that confirms Dr. Piness' statement concerning the time it takes for pollen sensitization to establish itself. I see a good many people who move to the San Francisco Bay region because of having had hay fever in the interior valleys of California. A few are comfortable for about two years. About the third year they begin to have symptoms. This emphasizes the futility of moving around for relief from hay fever. If a person is susceptible, he is apt to get it sooner or later in whatever community he lives. Of course the bay region, as I have shown in a botanical survey, is comparatively free from pollen compared with other regions, but even with the small amount of pollen there, many patients become sensitive. It takes two or three years to develop symptoms, and, if uncontrolled, the condition increases so that treatment becomes necessary.

DR. PINESS.—In answering Dr. Balyeat concerning the intelligence of these people, I want to say this: The people in the potash community are mostly college men. There is more research being carried on there than there is commercial work. It is true that some of these people are low in their vocational qualifications, but there are none in the community whom I know of who are illiterate. The same is true of this other mining town where approximately seventy per cent of all employees have had either high school or college educations. The object of this particular mining company is to train young men in the mining profession and then farm them out to other communities.

All these youngsters who started in the first decade of life are the children of individuals who have hay fever on either one or both sides of the family. Those gave the largest hereditary picture as well.

In answer to Dr. Sterling in regard to his number of injections, I want to set him right on that. These cases were all treated pre-seasonally and treatment was stopped with the onset of the season. Having had sufficient pollen survey over a period of three years, we anticipated a certain time of year when they would start their season and we hoped to complete our treatments. We gave these people 33,300 units of pollen antigen, and that is as much as you give even when you give injections as many times as you did. I do not know of anybody who gives a larger quantity. The number of injections given were approximately twenty, because we figured we would start them about three and one-half months before the onset of the expected season.

In answer to the point brought out by Dr. Rowe that individuals who acquire hay fever after moving from one community to another, I quite agree with his findings that symptoms occur any time from one to three years, sometimes longer. It is usually longer. We were not concerned with that particular problem. Nor were we discussing individuals who previously had had hay fever. We were discussing, at that time, individuals who never had had hay fever or a history of allergy before they came to this community and who started to have symptoms from the first to the third year.

A Survey of the Medical Schools of the United States Relative to the Teaching of Diseases Due to Allergy. RAY M. BALYEAT, OKLAHOMA CITY, OKLA.

It is contended that during the last decade at least 7 per cent of the population of the United States at some time during their lives suffered from some form of allergy. The situation seems to call for a more thorough knowledge of allergy on the part of the average practitioner. Such knowledge can best be supplied by a more adequate teaching of the subject in the medical schools of the country. A questionnaire sent to the professors of medicine of thirty-five of the leading medical schools of the United States, revealed the following facts:

In only eight schools is a definite number of hours being given to the study of diseases due to allergy. In these eight, the work is compulsory in six; elective in two. The average number of hours is eight. In four of the eight schools the work is given entirely in the junior year and in the other four, partially in the junior and partially in the senior year. In four of the schools the work is given in the medical department; in the other four in the department of bacteriology or immunology.

It is evident that such teaching is inadequate. Dr. Balyeat suggests a course to be given by a specialist in the field, along the lines of the course given by him in the University of Oklahoma. Eight lectures of one hour each are given junior medical students. The fundamental principles of allergy and its practical application are considered. During the senior year there are several clinics of two hours each, devoted to the teaching of allergy. This gives a total of from sixteen to twenty hours devoted to didactic and clinical work in the study of allergic diseases, compulsory for every medical student. There is furthermore, an elective course offered to the senior students consisting of sixteen hours made up of clinical and didactic work, chiefly, however, clinical. Such a course could be offered to students especially interested in the study of allergy.

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—In coming over on the train with Dr. Dean of Washington University and in discussing the subject with him, he told me that since he has taken a professorship at Washington University he has instituted in his department two graduate students who are full-time men at Barnes Hospital, who are going to devote their time to working out allergic problems.

Not so long ago Dr. Dean was not so enthusiastic about allergy. I think he now is inclined to give it considerable attention and through him I am sure with the institution of such an attitude in the nose and throat department of Washington University, courses will be instituted in other universities.

DR. F. M. POTTENGER, MONROVIA, CALIF.—I was very much interested in these papers this morning. The thing that strikes me is this: In the knowledge of medicine in the curriculum, I do not know where the teacher is going to stop. Dr. Balyeat said that in the University of Oklahoma eight hours out of sixty-four

are given to allergy, eight hours for tuberculosis, eight hours for heart disease, eight for the stomach. There is not much left for laying the general foundation of medicine. This is a tremendous field and it seems to me the thing that we need most on these subjects now is research work and getting a thorough foundation rather than making specialists of undergraduates. I think there should be in connection with every medical department men who could deal with this work, but I do not know just how much should be put in the curriculum.

I have been reading recently a very interesting book by Stockel on "Angioneuroses." There is not a thing that he has not classified under angioneurosis. He cured everything that Dr. Rowe has cured this morning, classified under angioneurosis.

There is a tremendous amount of work to be done here. We have to develop functional pathology to the same extent that we have developed anatomical pathology. This is just a part of the great field. That is where the greatest research in medicine should be done. I think correlation is more important. I do not know whether we would get so far if we increased the hours taken out of medicine. I should like to see the whole thing emphasized as a part of medicine but research is more important than anything else.

DR. BALYEAT.—I just wish to say in closing in regard to Dr. Pottenger's mentioning the eight hours, that we really have 132 hours of medicine, the other sixty-four hours being devoted to didactic and clinical medicine combined.

In revising our entire curriculum this year, the entire faculty spent two nights at it. The man on tuberculosis felt sure that eight hours was a very small amount to devote to a disease as important as tuberculosis, which is true. We decided to devote eight hours to allergy, eight hours to cardiology, and eight hours to renal diseases. When it was finally figured out there was plenty of time for the professor of medicine to lecture on the other things that were left out by those who were doing special work. This is the first year that we have really introduced it. We are not sure how it is going to work, but we think it is going to work out all right.

I really feel there is one other thing we should do if we are going to teach the medical profession that there is something to allergy. Last year Dr. Rowe had a paper on our general program. This year there is only one paper by Dr. Piness that I can find in going over the program on any phase of allergic diseases, and I feel that it is a mistake if we possibly can help it for us to go to a national meeting without being on the program.

Further Studies in Treatment of Food Sensitization with Digestant and Citric Acid.

ORVILLE HARRY BROWN, PHOENIX, ARIZONA.

The work presented in this paper is based upon the theory that whole protein gets into the blood stream and tissues of the body and is there digested by an enzyme "P." Two compounds result. One of these is a toxin which is further digested by a second enzyme "T" and possibly by a third enzyme "T" 2 or a fourth one "T" 3, until detoxication is complete. Enzyme "P" may be identical for two or more proteins, whereas "T" is probably specific for each toxin. It is possible also that the toxin portion of the protein may be absorbed from the alimentary canal. The toxins may accumulate in the body and produce chronic effects. In such cases, it seems impossible to rid the body of them, no matter by what method. The theory is presented for its worth and seems substantiated by many observations.

It is further suggested that there is inadequate digestion of proteins in the stomach and these pass directly into the tissues as whole or split proteins. Many extraneous conditions as colds, nervousness, etc., depress digestion, probably by reducing the hydrochloric acid. A high percentage of sensitization cases have low gastric acidities. This is exemplified in a table which is given of fractional gastric analyses on a series of patients.

Hydrochloric acid in conjunction with pepsin and calcium has been used by the author with good results in a large number of cases of allergic conditions. An organic citric acid was found to have as good an effect as hydrochloric acid. Two ounces of citric acid to eight ounces of water are made up. One to four teaspoonfuls in a glass of water is sipped with meals.

Case reports of severe pruritis, urticaria, eczema, asthma (food), bronchitis, flatulence, angioneurotic edema, migraine and trigeminal neuralgia are cited, and in each the use of acid appeared to relieve or greatly improve the symptoms. In some cases instructions as to proper eating and also a limitation of the diet to foods reacting with skin tests were supplemented.

DISCUSSION

DR. F. M. POTTENGER, MONROVIA, CALIF.—Doctor Brown's paper throws food allergy back to the internist. It seems to me that in this whole study we are getting to this fact: if we could just find out why food will pass through the intestinal mucous membrane undigested in one individual and not in another, and why pollens and other proteins will pass through the mucous membrane of the respiratory tract in one person and not in another, it would help us greatly in understanding the allergic problems.

The main point of Doctor Brown's paper is a recognition of the fact that if food is thoroughly digested, it is less apt to produce allergic phenomena and in this way he has been able to relieve a great many patients by using proper digestants. The tissues that permit the entrance of undigested protein must have an increased permeability. Recognizing this fact, there are two ways of opposing allergic reactions. One is to prevent the offending protein from coming in contact with permeable cells. This may be done by withdrawal if we know the particular food that is the cause of allergy. Another way is to digest food so that it does not enter the tissues in an undigested form. Still another method is to endeavor to take away this increased permeability and thus defend the patient from within so that he is not sensitive.

The problems are serious and their solution is difficult. This Society is doing a tremendous work in showing what the problems are and in helping solve them.

I am particularly interested in bacterial allergy. This is ever present in tuberculosis; in fact, it is the cause of practically all of the clinical manifestations of the disease. The same explanation is applicable to those cases of bronchitis which are dependent upon or which follow acute sinusitis. An infection in the sinus is nearly always followed by an exacerbation in the bronchi. We have spoken of it in the past as an infection going down to the bronchi. This is probably inaccurate. It is more likely that the disturbance in the bronchi is due to bacterial protein from the upper air passages gaining access to the blood stream and cir-

culating until it comes in contact with areas of previous infection in the bronchi, where it produces an allergic reaction.

DR. GEORGE PINESS, LOS ANGELES.—I think it is rather timely to hear something on the chemical aspects of this subject as relating to Dr. Brown's paper, and if the chair will extend the privilege, I am sure Dr. Alles would be glad to discuss it from the chemical standpoint.

DR. GORDON ALLES, LOS ANGELES.—I have not very much to say and whatever I have to say is from the viewpoint of the chemist and physiologist. This problem of sensitivity certainly is a very interesting one from the standpoint of a question that arises as to how far down in the stage of protein degradation do you still have sensitivity occurring. The question as to whether it must go down into the proteose stage or how far down in the scale of protein degradation one must go before failing to get compounds that will react anaphylactically is not known. Certainly when you get down to the stage of peptones you have compounds that no longer react anaphylactically. It seems a logical method of approach to the treatment of this general problem to attempt to digest the proteins more thoroughly.

The question as to whether hydrochloric acid is a useful method of aiding this, however, has many complications, for although the fact is certain that hydrochloric acid is necessary for peptic digestion of protein, we do not know whether other enzymes that one might wish to postulate require it. In the case of hydrochloric acid aiding the digestive action of pepsin, one might say that phosphoric acid and citric acid would also be likely to aid digestion. Use of hydrochloric acid might be objectionable from the standpoint that the increased acidity is associated with increased permeability. Aside from the possibility of hydrochloric acid aiding digestion, you would have a detrimental effect on the tissues in general, which instead of decreasing the allergic or, we will say tissue reaction, would increase such reaction very considerably in some cases, so that aside from a beneficial effect that one might expect from aiding protein digestion one must be extremely careful that he is not increasing acidity of tissues and getting a more severe attack.

I think Dr. Rowe's idea of attempting to use proteose and peptones in his treatment of food allergy is a very good one along exactly the same line without the possibility of bad reactions. So far as I know, the preparation of satisfactory proteose preparations has not been established from the standpoint of anaphylactic responses. I should very much wonder whether, perhaps, some of the proteose or peptone preparations that one might use might not still be able to engender certain anaphylactic reactions.

DR. WILLIAM DAVID SANSUM, SANTA BARBARA, CALIF.—For a number of years we have been doing work similar to that which Dr. Brown has done. We began with a case of food asthma in a child who was sensitive to all common proteins, making the use of elimination diets impossible. Our work on allergy is secondary to our general problem of adequate nutrition. When one decides what foods should be used in a given case, it is a serious handicap to find that the patient is sensitive to them. We believe, with others, that patients may be sensitized to undigested or incompletely digested proteins absorbed from the alimentary tract. Whenever we see an undernourished adult we usually find that he is underweight either from ignorance of nutritional requirements or from an inadequate digestion. The vast majority of them are underweight from faulty digestion. We have routine Ewald test meals done. If the hydrochloric acid is low, we have fractional Ewald test meals done. To correct this deficiency, we use citric acid in the form of grapefruit and lemonade. By using sufficient quantities one can obtain a hydrogen-ion concentration sufficiently high clinically to take the place of hydrochloric acid. Dr. Ivy has shown that citric acid is sufficiently strong to stimulate the flow of pancreatic juice.

For the intestinal types of indigestion we use enteric-coated pancreatin. Parke, Davis & Co. have recently succeeded in coating granules of pancreatin. Each five-grain capsule contains about two hundred granules. The gelatin capsule dissolves in the stomach; the protected granules mix with the food and as they pass with it into the intestines afford many foci from which digestion can take place instead of one as with their former panteric tablet. This capsule was devised especially for patients with achlorhydria, but it apparently works equally well in patients with normal and hyper stomach acidity.

We now have a long series of improved cases just as Dr. Brown has described, including food asthmas, hives, urticarias, angioneurotic edemas, and food eczemas. The last serious case which we had was a woman thirty-two years of age who had had eczema since she was two months of age. She was skin-sensitive to fifty-six of the sixty proteins for which we tested her so that an elimination diet was impossible. We did eliminate the worst offending foods, gave the panteric capsules and in six weeks' time the improvement was remarkable.

We have a number of cases of bronchial and pollen asthma which have improved. We have assumed that perhaps these patients become sensitive to the bacterial proteins and pollens which they swallow with their food.

It seems to me that this is a wonderful field in which to work and that it is full of possibilities. In attacking these problems from a digestive standpoint, it seems to me that Dr. Brown's work has a great fundamental value.

DR. ROBERT L. BENSON, PORTLAND, ORE.—I think Dr. Brown's consideration is a very fundamental one and I was much interested in Dr. Alles' discussion of this. I feel that there may be something of a chemical nature that is perhaps way below the stage of anaphylactic sensitization that should be worked out. Possibly this has to do with histamine. There is nothing new at all in that consideration. It seems to me we need help from the physiologist, telling us just what those substances are and what the physiology of them is, whether they are absorbed from the intestinal tract, and under what conditions. Possibly the rôle of constipation is going to become the most important fact in determining the conditions for the absorption of the low-grade protein disintegration products. On that supposition, I feel in the handling of our chronic cases, especially those with constipation, that before we can do anything in an allergic way to benefit our cases, we certainly must not lose sight of the paramount importance of first handling the chronic constipation; if possible in such a way that the patient is able to handle it for himself eventually, so that he becomes independent of catharties and artificial means.

DR. ALEXANDER STERLING, PHILADELPHIA.—Dr. Brown has mentioned the presence of achlorhydria. He failed to mention the age limit in all of those patients in whom he found achlorhydria. Were they young or old? That might make a difference in drawing conclusions from the presence or absence of achlorhydria.

Another question I should like to clear is this: Were all the patients studied from the standpoint of protein sensitivity and treated accordingly and then, when you failed to relieve them did you resort to digestants, or did you put them on digestants and acid treatment without an allergic study?

DR. ALBERT H. ROWE, OAKLAND, CALIF.—I want to say a word about this question of food allergy in relation to digestants. I have followed Dr. Sansum's work with a great deal of interest. I know if I could get the results I should like to get from the suggestions Dr. Sansum has made, I should not have to use the elimination diets that I have used in the control of cases of food allergy.

I did not have time to read the statistics in my paper this morning, but I have carried out stomach analyses on 30 of my 50 patients. Those cases had stomach analyses because I felt there was some indication for them, or because of the fact

that they were not readily controlled. Out of the 30 only 3 had an achylia and 4 or 5 had a hypochlorhydria. In those cases that had a deficiency of acid, hydrochloric acid was given in proper doses. I have given over 70 patients Sansum's triple pancreatin tablets or granules, one or two after meals. I have had a few helpful results and in one or two cases I feel there was a specific effect. In the others I did not get any result and I did not get any particular help from the use of acid, except where that help had been obtained already by elimination diets.

Of these three cases of achylia, two of them had been discovered before they came to me and had been treated with pepsin, hydrochloric acid, and various diets which other physicians had given them. I think the deficiency in acid has something to do with the establishment of protein sensitization in children. I think it may have something to do with the establishment or protein sensitization in adults, but I think overfeeding has a greater effect especially in infants before the membranes have attained a certain degree of impermeability. After sensitization is established, it often takes such a minute amount of the substance to produce the allergic reaction that acid or digestants cannot have any effect. In the individual reported by me this morning who was sensitive to garlic, we certainly could not have prevented his symptoms with acid or with digestants.

I think the work of Walzer in which he shows that one can demonstrate the presence of food proteins in the blood stream of normal individuals who take food after a fasting state, emphasizes the difficulty in preventing symptoms by acid and digestant therapy.

There is no question but that many people have a local sensitization in the buccal cavity, and I think in the esophagus, the stomach, and duodenum, as well as in the rest of the intestine. I do not think any digestants are going to destroy or break down the proteins rapidly enough so that such local symptoms can be prevented. It is a big problem and it needs the attitude which Dr. Sansum and Dr. Brown have taken, but I think food allergy cannot be satisfactorily controlled without a diet elimination method.

DR. BROWN.—I think Dr. Pottenger has hit the keynote of the problem in his remarks on tuberculosis in allergy. It does seem to me that there is a very definite relationship between inflammation and allergy; in other words, sensitization and allergy are a part of inflammation. We must consider them together. That inflammatory conditions seem to have some effect which renders a cell more susceptible to the reactions that we know as allergy, there is no doubt.

Early digestion seems to me to be important. That is why I have emphasized digestion in the stomach rather than digestion in the upper alimentary canal. I think both of them are important.

I was very much interested the day before I left home to pick up the *Journal of the American Medical Association* and read an abstract of Dr. Sansum's article on the use of grapefruit. I have made it more or less a routine to administer my acids through the medium of the citrous fruits. Once in a while a patient is sensitive to orange or grapefruit, less rarely grapefruit, which I think makes it inadvisable to use it routinely.

There are many cases of mixed sensitization, as has been mentioned here, in which it is not enough to cure the stomach condition or to cure the hay fever, but one must go further and get at most of the severe sensitizations and eliminate them.

Dr. Benson contributed a very important point which I did not mention: that is constipation. It seems to me that proteins that are partially digested have a better chance of being absorbed if they lie in one part of the alimentary canal too long.

In regard to Dr. Sterling's question, I do not treat my cases routinely. I like to study them thoroughly from all angles. I have to be governed by the patient's mental attitude or financial condition. I do not hesitate to use the acid empirically, perhaps without making a sensitization test, and some of the cases do not come

back for further study because of relief. I do not wish to mislead, however. Many of the cases are not benefited by the use of acid. It is the early case particularly in which you get most satisfactory results. In such cases as Dr. Rowe mentions in which there is a marked hypersensitive condition (garlic), I should not expect to get much benefit, if any, from the use of acid. The absorption of that garlic might take place even before it reached the stomach.

The Relation Between Bronchial Asthma and Pulmonary Tuberculosis.* ALEXANDER STERLING, PHILADELPHIA, PA.

This paper opens up an old controversy as to the association of pulmonary tuberculosis and bronchial asthma. The literature of the causal relationship between these two diseases is reviewed from the viewpoints that such a relationship does exist, and that it does not.

In order to get the opinion on this point, of many clinicians interested in tuberculosis, a questionnaire was sent out. Inquiry was made as to the percentage of cases of bronchial asthma that is encountered among patients with tuberculosis. An opinion as to whether tuberculosis was responsible for cases of bronchial asthma that were seen, was also requested.

Quotations from 14 replies are given. A summary of these indicates that the consensus of opinion is that tuberculosis is not an etiologic factor in asthma, and that the percentage of asthmatics with pulmonary tuberculosis is very meager. The author states that of 350 of his own case records of patients with bronchial asthma, only 5, or less than 1.5 per cent, had pulmonary tuberculosis with positive sputums. In addition, 15 patients, or less than 5 per cent, showed chronic pulmonary fibrosis without positive sputums, who are usually classed as tuberculous.

In cases of asthma with tuberculosis that showed hypersensitiveness, it was found that asthmatic attacks could not be readily controlled by desensitization unless climatic treatment for tuberculosis were carried out in addition. This is exemplified in two case reports.

The use of tuberculin as a satisfactory drug in tuberculosis is questioned. Its use in bronchial asthma is considered from the standpoint of a nonspecific protein.

DISCUSSION

DR. WARREN T. VAUGHAN, RICHMOND.—I think the problem in the minds of many of us is not so much whether tuberculosis causes asthma as whether asthma will produce tuberculosis; that is, induce an active tuberculosis in an inactive case. I think we have all passed the stage where we believe the former teachings that bronchial asthma is a protection against tuberculosis.

If I read Dr. Van Leeuwen's monograph correctly, I am under the impression that he did not present tuberculin therapy as a specific measure, but stressed, on the contrary, that he did not use tuberculin in cases with open tuberculosis, and that he recommended it as a nonspecific desensitizing agent.

*The complete article will appear in the author's reprint.

DR. ROBERT A. PEERS, COLFAX, CALIF.—When we get a definite case of bronchial asthma we refer the patient back to the local physician and advise him to have the patient tested for protein sensitization. We do have, however, cases with definite bronchial asthma with tubercle bacilli in the sputum. I think those cases are very rare. We have, moreover, patients referred to us who have been told they have asthma or who have reached that diagnosis themselves because of their shortness of breath and other asthmatic symptoms, but they do not have true asthma. Their asthmatic symptoms are due, largely, to cicatricial tissue formed during the slow development of their tuberculosis.

What Dr. Vaughan spoke of reminds me of two cases I saw that were very interesting to me because they showed mistakes on my part.

A number of years ago a patient was referred to us because of tuberculosis. She had a very definite bronchial asthma. Although we gave her a complete examination, including tuberculin tests and an x-ray study, we could find no evidence whatever of active tuberculosis. We referred her to a physician who gave her various tests for allergy. We saw her about a year later with a very advanced tuberculosis, with numerous tubercle bacilli in the sputum and the x-rays showed advanced tuberculosis. When comparing the x-ray plates you would not think it possible that they could have been plates of the same person.

We had another case of a woman who had had asthma for many years. This was several years ago. She was examined by us at her request and we failed to find any evidence of active tuberculosis, although there was evidence of what we considered to be at least old healed tuberculosis. Less than nine months following the report which we gave her that she had no evidence of active tuberculosis, she became very acutely ill with what she said was ptomaine poisoning. Her symptoms seemed to be abdominal in origin. She began to cough. She saw a physician who had an x-ray plate taken which showed a large basal cavity. There were no tubercle bacilli in the sputum and he said she had a pyogenic lung abscess. Later, there were numerous tubercle bacilli in her sputum and she had a very rapid case of active tuberculosis occurring just a few months after we had made a negative diagnosis.

DR. F. M. POTTENGER, MONROVIA, CAL.—Tuberculosis and asthma may develop in the same individual, as we often see. They are not antagonistic as has so long been taught; at the same time the individual who is subject to asthmatic attacks probably has a different cellular and nervous reaction from the one who is subject to tuberculosis. Much light will probably be thrown on this question by the work of the constitutionalists.

The type of tuberculous patient that, as a rule, shows most asthmatic signs is the slow-going fibroid type. We do not find it so much in the more acute type, which is accompanied by exudative phenomena. Many cases of tuberculosis do not have a real definite asthma with acute paroxysms, but a type of breathing similar to that of the asthmatic, only of a milder degree. Whether this is a reflex effect through the vagus nerve, or whether it is due to the tuberculoprotein causing a reaction in the bronchial tissue, is impossible to say. One thing is very definite. The allergy produced by such bacterial proteins as those derived from the tubercle bacillus and exhibited in all chronic tuberculous foci, and that produced by the streptococcus, as we see in rheumatism, do not cause symptoms of asthma, but a more lasting allergic inflammation which is responsible for the disease picture which develops.

DR. GEORGE PINESS, LOS ANGELES, CALIF.—With regard to the question of desensitization of the tuberculous, I do not believe they should be. I feel as Dr. Pottenger does, that as the toxemia increases, particularly with the rise in tempera-

ture, they rarely have asthma. This is an interesting thing. Dr. Pottenger and I once had a patient who had tuberculosis as well as bronchial asthma; two separate distinct entities. Neither was dependent on the other. This young man would infect himself in local areas to acquire a temperature and he would be free of his asthma during that time. He got so that he had a series of furuncles on his arm all the time.

The individuals who come to us supposedly with bronchial asthma and are tuberculous, are usually of the fibroid type, and it is purely a mechanical dyspnea and rarely the spasmodic type. They do have this same dyspnea on exertion or after laughing or after eating. It has no relation to their sensitivity. They are not of the sensitive type.

DR. PHILIPP SCHONWALD, SEATTLE.—In view of what Dr. Vaughan and Dr. Pottenger have mentioned, I should like to relate a case of tuberculosis and asthma that I had a few years ago. It was a relatively young man of some thirty-odd years, who had had a very severe constant asthma for four years. Food tests gave no information at all. His family physician, however, insisted that he had tuberculosis, although the x-ray picture was more or less negative, showing a slight fibrosis in the hilus region. It was impossible to investigate for râles because he always had a very loud wheezing in his chest which made it impossible to discern any finer noises.

He finally went to an institution in Denver for two or three months. Active tuberculosis was not found there. His sputum was examined many times in that institution and was always negative. He came back and got into the hands of an osteopath in Seattle who had a large practice and was treating asthmatics by a starvation cure. He was submitted to a very severe starvation of about twelve days' duration. His asthma did not get better. He lost enormously in weight. Shortly after that I found tubercle bacilli in his sputum. He died several months later of advanced pulmonary tuberculosis. He had asthma up to his last breath.

After the statement Dr. Vaughan made, we are interested in knowing whether asthma will change inactive tuberculosis into an active process. It would be, of course, false in this case to conclude that, because it was the starvation that brought about the change, at least to my belief. On the other hand, although he had a very active and progressive process after that, his asthmatic attacks did not stop.

I wish to mention also that I tried to treat that man with tuberculin. It was about the time when Van Leeuwen came out with his publication as to the treatment of asthma with tuberculin. In this case positive sputum test had proved that the man had tuberculosis. The tuberculin treatment was of no avail.

The only instance where I believe I saw a good result from tuberculin treatment of asthma was in the case of a little boy about twelve years old who was the son of a tuberculous mother. He had a definite enlargement of the hilus glands and had an asthma, but did not run any temperature. He was treated with tuberculin, very small doses, and cleared up in two months. He has had no asthma since, that I know of, and no tuberculosis.

DR. STERLING.—I visited several tuberculosis clinics where quite a number of patients who were treated for tuberculosis actually belonged to the asthmatic group. In one place I found four asthmatics who did not belong in the pulmonary tuberculosis class at all. In another instance I examined seven of them. Three were asthmatics.

I wonder whether it is justifiable to use tuberculin in those patients who do not improve by desensitization or vaccine treatment. We meet with a type of patient

that does not show a tuberculous involvement, but there is present a chronic fibrosis which may be a deciding factor in the asthmatic syndrome. The question is, shall we use tuberculin treatment, as suggested by those who do think tuberculin treatment vital or shall we not? Personally, I am still afraid to use it.

The Effect of Allergic Reactions on the Course of Nonallergic Diseases.* WARREN T. VAUGHAN, RICHMOND, VIRGINIA.

At the outset of this paper, the point is made that as the field of allergy widens, specialists are developed to deal solely with this condition. Despite the contention by others that an allergic individual is likely to be otherwise in exceptionally good health, it remains a fact that he is exposed to all the diseases that fall within the domain of internal medicine, and a broader viewpoint of the allergist thus becomes necessary.

Attention already has been called to the deleterious effect that pathologic nonallergic processes may have on the course and treatment of allergy. The present paper deals with the reverse condition, namely, the effect of allergy on nonallergic diseases when the two are associated. This is exemplified in three case reports.

The first case is that of a woman with allergic eczema of the hands which remained intractable to treatment for three months. Then it was suspected that she had an associated hypothyroidism, which proved to be the case. Treatment with thyroid extract cleared up both conditions. Nevertheless, subsequent contact with the specific allergen produced a return of the eczema, although the patient was still taking thyroid extract. The point is made that in this case one cannot be certain which condition was dominant, and it is quite as possible that the hypothyroidism retarded the treatment of the allergic eczema, as otherwise. Apparently both factors were active.

The second case is that of a woman who at twenty-three had a high blood pressure. At thirty-one the systolic pressure became fixed at 170 mm. Hg, and this gradually increased to 200 mm. There was an associated cardiac hypertrophy, and at thirty-four decompensation first appeared. One year later typical cardiac asthma developed. It was then found that there was a coincident sensitivity to feathers and also to several foods. With the use of a floss pillow, cardiac asthma disappeared for four months. Then decompensation recurred and persisted until death. It is noteworthy that the associated attacks of acute pulmonary edema responded to ephedrin better than to morphine and atropine. The case suggests that an acute allergic reaction induced attacks of acute pulmonary edema associated with cardiac failure. The acute pulmonary edema was not to be confused with bronchial asthma. This seems confirmed by an experience wherein the initial symptoms of pulmonary edema would always occur in one particular movie house and not in others.

*The entire article will appear in the author's reprint.

The third case concerns a child of seven with pulmonary tuberculosis, and an associated pollen asthma. Improvement of the tubercular process was notable during the winter months, with reactivation in the pollen season and again improvement thereafter.

It is recalled that some cases of migraine and mucous colitis responded better when the allergic factor was controlled.

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—This paper of Dr. Vaughan's brings up some very interesting factors in connection with diseases other than allergic ones, but in which allergy complicates the picture. The cases reported by Dr. Vaughan are those seen by every one of us, not infrequently but commonly.

I think Dr. Joseph Pratt in 1925 brought out a group of cases of so-called cardiac asthma. In that group he definitely presented a picture which was not allergic. I had the pleasure of discussing that paper and at the time suggested to Dr. Pratt that the symptoms of a cardiac asthma were so characteristic that they did not lead one to believe that he was dealing with a regular bronchial asthma. The cases he presented were individuals past middle life, who were perfectly all right with the exception that they had a slight dyspnea on exertion, and that their attacks of so-called asthma occurred usually during the night. The patient awakens because of pressure in the chest, precordial pain, rushes to the window for air, and then feels somewhat better. Occasionally he requires morphine and atropine and then obtains relief. These patients, opposed to Dr. Vaughan's case, were not relieved by the use of drugs, such as ephedrin or adrenalin, during the attacks.

The case of Dr. Vaughan's is similar to some that I have seen in the past few years that have had their hypertension over a long period of time, and regardless of their asthmatic attacks would have cardiac involvement. This particular case that Dr. Vaughan speaks about, that I happen to know of, is interesting because of her lack of cooperation with her doctor. She realized her difficulties, but apparently was not the type that would assist her doctor in trying to keep her well. I happen to know that on one trip from Washington to New York she decided that her silk floss pillows did not mean anything. She slept on the feather pillows in the train and had her usual attack.

With regard to the question of metabolic rates in asthmatic or allergic individuals, in my own work we have done metabolic rates particularly on the heavy or adipose individuals and found that there is no relation of the metabolic rate to their allergic disease. However, some of them are definitely hypothyroid, and there are also some who are hypopituitary.

I do not believe, nor have I been able to prove that treatment for the endocrine disturbance has any relation or any bearing on the results obtained in the allergic disease.

The cases of migraine reported by Dr. Vaughan are quite similar to those that we all see. The few allergic migraines that I have seen I reported some seven in number in 1924. They had definite allergic histories. Every one that I have seen up to the present time has had some complicating allergic condition and migraine disappeared with relief of other symptoms.

I want to ask Dr. Vaughan whether in the case of tuberculosis he reported the asthma disappeared with the recurrence of the tuberculous condition, that is, with the onset of temperature?

The question of this woman having her attacks in the cinema is a rather interesting one because I am just getting ready to report on an asthmatic death, a man who was an aviator in the Canadian Army who had had hay fever in his early life. After his enlistment in the Air Service of the Canadian Air Forces he

went overseas without trouble. He came back after a crash and had plastic work done with a very good result. Then he began to have his hay fever and asthma attacks again. He always knew that face powder gave him trouble, but apparently there was no connection with the recurrence of his condition and face powder etiology.

He was sent to Dr. Pottenger's Sanatorium. Then Dr. Willard Stone saw him and then I saw him, but I was not in a position to study him. His history was interesting. He went to a certain motion picture theater in Los Angeles and had an acute attack of asthma. It took twenty-four hours to bring him out of the attack by injections of adrenalin, morphine and atropine. Being rather curious, he decided he would go back to this theater again a month later. He had another attack of asthma. I saw him at eleven-thirty in the morning in consultation with Dr. Montgomery. He was moribund at the time. He died at twelve. We obtained permission and performed a postmortem on him. One saw the typical picture of an anaphylactic guinea pig's lung. The pathologic picture was characteristically that reported by Huber and Koessler.

The picture was such an interesting one that I decided to investigate further. The patient's wife told me that whenever they used insect powder in the house he had to leave. I then went to the moving picture theater and found that they used an insecticide on all their velvet curtains and velours. If any of you have noticed it, in a theater you get a sweet odor that suddenly comes through the house, which seems to be an antiseptic of some kind. We found that the particular one they used in this theater was made of a saturated solution of pyrethrum. Of course, the question came up whether or not somebody sitting next to him had shaken his coat or whether some woman had powdered her face and he got a load that way. However, I believe the cause of his death was probably pyrethrum.

DR. RAY M. BALYEAT, OKLAHOMA CITY.—I want to ask Dr. Vaughan a question or two. He got me into trouble about three years ago. I went to Virginia where he was seeing a lot of eczema, urticaria and migraine, so I went home quite interested in them. I had not been doing anything except asthma and hay fever before that. I began to see so many eczemas and urticarias that I did not know what to do with them and we are still seeing more than we want to see.

I feel without any question that it is up to the men doing allergy to take care of the migraines and urticarias. We will be able to do more (although we will not do for the urticarias what we will for hay fever and asthma) than the other men dealing in the field of medicine. I feel pretty confident of that. These cases certainly need dieting, even if we do not find them positive, as happens in a great many cases. I believe in treating migraine at the present time we may get good results in 40 per cent of the cases, and if we can do that, that is better than the other men are doing.

I want to ask Dr. Vaughan whether he is doing metabolic rates on the urticarias. At Asheville last fall, a man from New Orleans whose name I cannot recall, read a paper on urticaria in which he placed much emphasis on the metabolic rate. On arriving home this last fall I started to do metabolism tests on these people. There is no question but that the urticaria patients have in 60 per cent of the cases, at least, a low metabolism, a great many of them ranging from minus fourteen to eighteen. We believe without any question in many cases that thyroid and calcium, or thyroovarian extract in women, will benefit their urticarial condition.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—Of course the work I have been doing in food allergy during the last two or three years has a very direct bearing on what Dr. Vaughan is talking about this morning. In fact the paper that I presented yesterday is filled with instances of the importance of taking into consideration the allergic factor in other conditions than just the common allergic phenomena that we ordinarily recognize.

I feel in regard to the conditions that I described yesterday—urticaria, angioneurotic edema and migraine—that it is possible, with diet control and by not depending entirely on skin reactions, to get good results in better than 40 per cent. Certainly I have a series of some 75 or more cases of migraine that I have seen during the last two years in which the results are better than 40 per cent—I should say nearer 75 or 85 per cent. These results have been checked by careful control.

I think it is going to be important for every internist, and particularly for the gastroenterologist, to take into consideration the allergic factor in all his work. I am very sure that many gastrointestinal symptoms are due to food allergy which is not being recognized today. I think one of the reasons, as I have stated before, is that we are trying to depend too much upon skin reactions. We are not recognizing the fact that, as Alexander says, food allergy expresses itself in a local manifestation. We cannot expect the skin to show the whole story. It may occasionally, but it is so much easier to work out the problem by diet elimination.

I see many internal medical problems other than those I have mentioned. I am sure if a doctor takes the allergic viewpoint into consideration and goes into the allergic history that he will often find manifestations of allergy that will help him in all kinds of medical problems.

I recall certain diabetics that have come to me who have been on prescribed diets including eggs or milk to which they are definitely allergic. The doctors who have controlled them before have insisted that these foods be kept in the diet, with production of symptoms that were very annoying. I recently saw a woman with hypertension. Along with her hypertension was a migraine and a gastrointestinal problem which were definitely allergic and which were relieved by the control of the food allergy.

DR. SAMUEL H. HURWITZ, SAN FRANCISCO.—I believe that Dr. Vaughan's paper merits particular discussion from the point of view of the very interesting way in which he has emphasized the relationship between internal medicine and allergy.

For many years I had the feeling, and I still have that feeling, that to be a good allergist one must be a good internist. To approach the field of allergy primarily through the gateway of allergy, I believe, is going to lead us into great error. We must not forget the whole in viewing the part.

I know in the organization of the Allergic Clinic at the Stanford Medical School, of which I have charge, we particularly stress this point by making it absolutely obligatory for every patient entering our clinic to have had a thorough physical examination by a good general internist prior to coming under our care. We feel just as has been contended for surgery, that surgery is simply a method of therapy, that a surgeon to be a good surgeon must also be a good diagnostician and a good internist, so I believe we will gradually come to the viewpoint that to be a good allergist one must be a good internist. At least, in working in the clinics it is possible for a patient to get a proper general physical examination, in addition to the particular technic which the allergist is gradually developing. I think it is a mistake to neglect the general medical problems.

I wish to say a word on the relation between the endocrine glands and the allergic constitution. I am not experienced sufficiently to say that endocrinology can explain many instances of the so-called allergic symptoms, but certainly in some instances there is a definite relationship between the deficiencies of the endocrine glands and a train of syndromes which simulate in every way those we recognize in the hypersensitive patient.

Not so long ago I recall treating a man who had had a general medical examination and in whom I am sorry to say the internist had neglected to diagnose a very obvious myxedema. The basal metabolic rate of this particular patient was minus thirty. The patient had symptoms simulating perennial hay fever and was

not sensitive, so far as we could determine by careful routine cutaneous test, to any allergic substance. The administration of thyroid, bringing the basal metabolic rate to within normal limits, relieved that patient very definitely.

It is not too far reaching to infer that the same myxedematous condition which prevails doubtless in the subcutaneous tissues also prevails in the tissues underlying the nasal mucous membrane.

DR. VAUGHAN.—In answer to Dr. Piness' question whether the asthma disappeared with the recurrence of the tuberculous condition in the patient that I reported, I would say no. The child had a recurrence of fever with the onset of asthma and the physician asked me to test the child to see whether she was sensitive to any of the pollens. We found her sensitive to the pollens mentioned. At that time she was still running a fever. We instituted pollen desensitization in spite of the fever and the asthma gradually cleared up and the fever subsided. It seemed to me to be quite a clear-cut case.

Thirty years ago it was taught that there were three kinds of asthma: cardiac asthma, bronchial asthma, and renal asthma. Fifteen years ago there was only one kind of asthma: bronchial asthma. The other conditions were called acute pulmonary edema and uremia. Today I should say there are very definitely three forms of asthma. The renal asthma is entirely different and due to acidosis, and is quite similar to the rapid, shallow breathing of a diabetic acidosis. The renal acidosis may be much higher than the diabetic acidosis. Then there is bronchial asthma with which we are all acquainted, and cardiac asthma with acute pulmonary edema which is altogether a different picture. Any one seeing this third case reported would recognize it at once as being altogether different from bronchial asthma.

The bronchial asthmatic is interested in getting his breath. He will sit up straight and bring the accessory muscles into play, throw his head back trying to get air. The cardiac asthmatic with pulmonary edema is interested only in one thing and that is getting up the bloody froth. He will bend forward coughing up this bloody mucus, which has to be wiped away from his mouth. That is altogether a different picture. The character of the material that is raised is all that is necessary to distinguish the two. I would agree entirely with Dr. Balyeat on his percentage of migraine results. He said 40 per cent. I have been through my series of migraine cases and in 37 per cent we obtained definite evidence as closely as one could, following Koch's postulates applied to allergy; namely, an allergic factor of migraine with relief on the avoidance of offending proteins. The postulates would be adapted to allergy by the following: first, the finding by positive cutaneous reaction to the offending protein, relief by its avoidance, and the bringing on of symptoms by subsequent exposure.

I would urge Dr. Balyeat to keep on with his eczemas. One does get too many of them and often wishes they would not come, but all of my eczemas (I say all, practically without exception) have already been to the dermatologist, and sometimes to several dermatologists. Those that we get, as a rule, are cases that have not responded to the usual accepted dermatologic methods, and when we can give them relief, we are giving relief where other methods have failed, and even a small percentage, 20, 30, or 40 per cent of success with them means a much higher percentage if we could see them all before they had obtained the relief which the dermatologist undoubtedly is able to give with other methods.

With regard to the metabolic rate in urticarias, my usual procedure is to skin test them first and if they do not respond satisfactorily, we run a metabolic rate; and third, if I do not get results that way I check them thoroughly for foci of infection, nonspecific factors, etc.

Urticaria is still the bête noire of the allergist, more than anything else. I had one very interesting case recently of a woman with chronic urticaria, her skin being

sensitive to several proteins, I do not recall which, who obtained no relief whatsoever on protein avoidance or nonspecific desensitization. Her metabolic rate was normal. She had a rather profuse endocervicitis. We cauterized the cervix as a routine procedure. With cauterization of the cervix her urticaria disappeared for two months and then returned. Her leucorrhea had also returned. We again cauterized the cervix with relief of the urticaria, again, and also a third time. A little infection flared up with a return of the urticaria. We completed the cauterization on the third treatment. It has been seven months since the last treatment. She has had no leucorrhea and no urticaria and considers herself well.

I present this case just as an example of the fact that allergy, in the strict sense, is not the whole story. We must consider the patient as a whole and all of the interesting factors that may be playing a part in the causation of symptoms.

Systemic Histamine-Like Reactions in Allergy Due to Cold. GEORGE E. BROWN AND B. T. HORTON, ROCHESTER, MINN.

Six cases are reported which exhibit local and general symptoms of cold allergy. The local effects on the skin were: pallor during the period of exposure, followed by redness, swelling, and increased heat of the hands after removal from the cold. Following a latent period of three to four minutes, a characteristic systemic reaction appeared, which was characteristic of that produced by histamine. There was a fall in blood pressure, a sharp rise in pulse rate, flushing of the face, a tendency to syncope, with transitory recovery in fifteen to thirty minutes. Complete recovery from the local reaction occurred in twelve to twenty-four hours. The experimental work which was carried out gave evidence of the chemical nature of these reactions, and strongly suggested the release of a histamine-like substance in the skin following exposure to cold. This substance, when carried in the general circulation, produced a reaction characteristic of histamine. These cases are amenable to treatment. By daily immersion of the hands in cold water, decreasing in temperature, for increasing periods, excellent results may be obtained. These clinical observations are further confirmation of the work of Lewis and his associates on the presence of histamine or allied substances in the skin of human beings.

DISCUSSION

DR. SAMUEL H. HURWITZ, SAN FRANCISCO.—I feel that the subject of allergy is already so complicated that to introduce new factors, the exact nature of which are so little understood, would make the subject still more difficult for many of us who are trying to unravel it.

On the other hand, there does seem to be a very vague relationship between the vasomotor reactions that one sees following exposure to cold and heat and some of the early manifestations on the skin in response to allergenic substances. I think the best work that has been done recently on the related subject has been by Sir Thomas Lewis and his coworkers. In his book published a year or so ago he presents instances of allergic response following not only exposure to heat and cold, but also to various traumatic agents and other irritants. Of course there may be, as he argues, a chemical substance liberated in the tissues as a result of the con-

tact between the cells and this traumatic agent, cold or heat or electric current. Whether it is of a histamine-like nature or not, is very difficult to say.

On the basis of Lewis' observations and those of Ramierez, we have made it routine to use histamine injected intracutaneously as a test for the allergic constitution. Dilutions of this substance are given although the history and other clinical responses may not suggest the allergic state whatever.

My impression from the phenomena described in this paper is that the response here was more analogous to the vasomotor reactions as we see them in Raynaud's disease and in some other vascular conditions, as Berger's disease, in which the sympathetic control of the vasa vasorum plays a very important part and doubtless reacts in an explosive way on contact with these various physical agents.

DR. ROBERT L. BENSON, PORTLAND.—I was interested in Dr. Horton's paper. It seems to me this gives the answer to the phenomena that Dr. Duke has been writing on for the last few years. I believe that it is approaching the problem in a logical and scientific way to treat it as a histamine phenomenon.

I wonder whether this does not connect up with the observations of a good many of us that certain individuals, whether they are allergic or not, upon going into cold water in the ocean always experience a general depression, lowering of blood pressure, headache, and symptoms that, in general, fit in with the symptoms of histamine poisoning. While it may be beside the point in this discussion, I should like if you do not mind, to call attention to what I think would be a good routine procedure in all our examinations. The question so often comes up, especially when we get negative reactions to our antigens, whether a patient is in a state of nonreactivity. So I make a practice in those cases of having a one to one thousand histamine solution, ergamin phosphate, and doing a similar test, which in my case is the scratch method and putting down a definite rating and the size of the reaction I get. In that way I know whether the patient is in a stage of reactivity or a stage of nonreactivity.

DR. JOHN P. HENRY, MEMPHIS.—Not so long ago I saw a young man about twenty-one years of age who complained of urticaria. Large wheals appeared whenever his body temperature became the least bit elevated. We are all familiar with this type of case as Dr. Duke has written so much about it. The treatment is quite a problem. This young man was a shipping clerk and when he would lift a heavy box or otherwise exert himself large wheals would appear over the entire body. The day I saw him his skin was perfectly clear. He said, however, that he could produce the urticaria at will and this he did in my presence, after taking off all clothes above the waist. By bending over and touching the floor with the hands and then assuming the erect posture, he was able to produce many wheals after repeating this maneuver five or six times. He had learned that cool water would stop it quicker than any other remedy. The urticaria would also disappear with rest. Sometimes these patients find means of curing themselves. This man had played on a basket ball team but had stopped on account of the urticaria. He was very fond of basket ball, however, so decided to play one night regardless of the amount of urticaria produced. This he did and after playing for a minute or two he was covered with urticarial wheals. Instead of stopping, however, he kept right on and played throughout the game. Since that night he has never been troubled.

Shortly after this I saw a young lady who had the same condition except that her skin was affected apparently by both heat and cold. When her body temperature was elevated above normal she had urticaria, but apparently she was sensitive to cold also because lowering the body temperature or exposure to cold would produce the same condition. Because of the fact that the first patient seems to have overcome his urticaria by exhausting the skin or by some other means not under-

stood, I suggested that this young lady try a similar procedure, but she states that she has tried to play tennis and if she persists after the wheals have developed, there seems to be a generalized edema with loss of voice and a feeling that she is going to faint. I then suggested that she go to the other extreme, but a cold shower or other exposure to cold will produce the same results.

Although the precipitating cause in both these cases seemed to be heat and cold, each was tested with foods, animal epithelials, pollens and miscellaneous products with negative results.

DR. WARREN T. VAUGHAN, RICHMOND.—I should like to ask Dr. Hurwitz whether he found that the histamine test gave any reliable information as to the presence or absence of an allergic state.

I should like to ask Dr. Benson whether he found that he could determine by the histamine reaction whether an allergic condition was in a nonreactive state.

I may not have heard all that he said, but as I understand it both used the histamine reaction for these two purposes, but I was not clear whether they placed much reliance on it.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—The question arises in the minds of all men interested in allergy whether there is an underlying allergic factor in these cases that has not been demonstrated, and whether or not the cold or the heat or other physical stimulus excites the urticarial manifestation of an underlying allergy. I saw a child recently who had hives whenever she sat in front of the fire. We tested the child and obtained no skin reactions. We put the child on an elimination diet and found a definite allergy—egg and wheat sensitiveness. We took the child off those foods and placed her in front of the fire on several occasions and the hives did not recur. I think the same problem comes up in dermographia.

It is very important in these cases where there is a question of physical allergy to be absolutely sure about the presence of an allergic condition which may not be demonstrated by the skin reaction—and we know that that definitely occurs.

I have an interesting case of angioneurotic edema that came to my mind while Dr. Horton was talking. A woman came into my office with a tremendous angioneurotic edema of the hands. At the same time she had a very flushed face. She told me she was having a hot flush and that she was just beside herself because of this tremendous reaction. She proved to be food sensitive. When we eliminated wheat especially to which she was sensitive the whole phenomenon disappeared.

DR. GEORGE PINESS, LOS ANGELES.—Dr. Rowe brought up something I had hoped would not come in this morning, that is to say the so-called physical allergy is a food sensitivity. I am not convinced, nor do I believe that physical allergy is an allergic phenomena. I am inclined to believe that it is a misnomer and should not be classed as physical allergy.

The same question comes up with angioneurotic edema as brought up by Dr. Rowe. I think it is about time that we decided whether or not angioneurotic edema is an allergic thing or whether we are really dealing with a giant urticaria. My opinion of angioneurotic edema is this: We can divide this syndrome into two definite groups, the so-called Quincke's edema which is not an allergic thing and the so-called angioneurotic edema which is nothing other than a giant urticaria and in the majority of cases an allergic syndrome. The so-called Quincke's edema is not allergic because of its clinical picture in that first of all the patient has attacks usually at the same time of the day, usually without itching. It usually comes on without the patient's realizing that the symptoms are approaching and they disappear over a period of time from a few minutes to twenty-four hours or more; whereas the true giant urticaria occurs rather suddenly. The patient realizes that something is happening. It is usually associated with itching and, as a rule, can be attributed to some definite factor.

As far as the physical allergy is concerned, I do not believe that such a thing exists as an allergic phenomena. It is a rather interesting condition of obscure etiology. However, I doubt whether it falls into the line of work in which we are particularly interested.

DR. ROBERT L. BENSON, PORTLAND.—In answer to Dr. Vaughan's question, the test with a standard solution of histamine is not, in any sense, a test as to whether the patient is going to react to allergy, but it is simply a test of whether the patient is in a state where he would react if he has any sensitization.

The normal thing is that every patient who is not, for some special reason, desensitized to histamine will react. Somebody recently published an article in which the histamine reactions were rated positive, but classified as strong, medium, and weak.

The thing I had in mind was this: A patient may have had adrenalin without knowing it and in the case of administration of adrenalin we are going to have interference with skin reactions. The best indication I can get whether the patient has had adrenalin and as to whether it will interfere is to do a test with a known solution of histamine. I find that a one to one-thousand solution of ergamin phosphate will produce a reaction wheal about the size of a dime, sometimes smaller, sometimes larger.

DR. SAMUEL H. HURWITZ, SAN FRANCISCO.—In answer to Dr. Vaughan's question, I wish to say that because of the fact that Lewis and his coworkers have found that histamine exercises a very marked effect upon the neurocirculatory mechanism, which is part of the skin test, that it might be worth while using histamine not really as a means of finding out whether there is an allergic state present, but whether the patient has the fundamental neurocirculatory mechanism which participates in the wheal. I have not found with histamine that one gets the particular exudation of lymph that one gets with sensitization of a protein substance. One gets the arteriolar flare very strikingly with a high dilution of histamine. Personally I prefer to use a dilution of 1:5000 rather than 1:1000 for the reason that I found that the neurocirculatory mechanism of the normal skin will respond very strikingly to a 1:1000 dilution, so that one cannot use that dilution as a criterion of differentiation. A 1:5000 dilution of histamine contains much less of the irritating substance that stimulates the neurocirculatory mechanism. We frequently find that patients who are sensitive to many substances have a more sensitive neurocirculatory mechanism as disclosed by an injection of 1:5000 dilution of histamine than has the normal individual. I have not any statistical data on the measurements of these tests. The information was obtained from a large number of patients over several years.

DR. ALEXANDER STERLING, PHILADELPHIA.—I have a very interesting case to recite which happened several years before Dr. Duke came out with his suggestion as to the presence of physical allergy.

A young girl, a milliner, had been suffering for many years with the appearance of an angioneurotic edema both in the morning and evening hours. The story as I recall it is that as soon as she left her home to go to her store she would get a swollen chin, cheek, and face, so that she had to unbutton her collar. By the time she reached her store, she was a sight. She attributed her symptoms in the winter months to cold and in the summer months to heat. At night after her supper she was afraid to take a bath, for each time she took a bath different parts of her body swelled with hives. That kept on for four or five years. I found that she was positive to six or seven foods which gave very large reactions. I checked up with her on the breakfast and evening foods she was eating and found she was sensitive to many. She improved when she discontinued those foods. The swelling

and angioneurotic edema cleared up entirely. Had I read Dr. Duke's report at that time I would have thought it was physical allergy and I would not have tested her through.

DR. B. T. HORTON.—So far as we were able to determine from the studies carried out, these patients whom I have reported were entirely negative to food sensitiveness or to pollens. We tried to place them in the physical allergic group, but whether or not we succeeded in doing so I am unable to say.

Allergy in Its Relation to Bee Sting. ROBERT L. BENSON AND HERMAN SEMENOV, PORTLAND, OREGON. (For original article, see page 105.)

A Botanical Survey of Memphis, Tennessee, and Surrounding Territory. JOHN P. HENRY AND A. L. HERRING, MEMPHIS, TENN. (For original article, see p. 163.)

Department of Reviews and Abstracts

Selected Abstracts

So-Called Fatal Anaphylaxis in Man, with Especial Reference to the Diagnosis and Treatment of Clinical Allergies. Lamson, R. W.: J. A. M. A. **93**: 1775, 1929.

This paper supplements a previous one on the subject published in 1924. It was concluded then that the exact mechanism of sudden death in the cases reported is not easy to define. There is some evidence that the serum injected played no specific part in the death of the patient. In a few of the cases the amounts injected were so minute that it is difficult to believe that the nature of the injected substance could have had much to do with the fatal result. One is inclined to assume some individual peculiarity on the part of the patient as the determining factor. Finally, a negative skin test may not be an absolute index of the reaction capacity of the patient.

Since 1924, additional cases have occurred. Three collected cases are reported. The first was an allergic individual of thirty-four years with hay fever. The only previous parenteral injection was typhoid vaccine which was followed by no untoward effect. Sensitivity to various pollens especially to Bermuda grass was established by skin reactions. Extracts of this pollen were given in 14 graduated doses with no untoward effect (0.4 c.c. of a 1:1000 dilution was reached). The next injection was 0.1 c.c. of 1:100 dilution. This was followed by some nervousness and insomnia but no other symptoms. The next dose was therefore reduced to 0.05 c.c. of 1:100 dilution. Immediately the face flushed, there were athetoid movements of the extremities, marked respiratory difficulty and the appearance of frothy bronchial secretion. From three to five minutes after the injection respiration stopped despite heroic measures.

The second case, a bronchial asthmatic, succumbed within ten minutes or so after intradermal skin testing. A positive reaction to buckwheat in a dilution of 1:500 was obtained at that time.

The third case, a boy of fifteen, who had been subject to attacks of asthma since early childhood died immediately after the injection of 1500 units of tetanus antitoxin.

Comment is again made that although dyspnea accompanied the fatal termination in these cases, the material injected was so minute that they should not be classified definitely as anaphylaxis until the mechanism of this reaction is better understood. A plea is made for organized study of these reactions.

Sodium Ricinoleate in Allergic Disease of the Intestinal Tract. Morris, R. S., and Dorst, S. E.: Am. J. M. Sc. **178**: 631, 1929.

Patients with intestinal symptoms associated with hypersensitization to intradermal injections of heat-killed intestinal bacteria were treated by daily administration of castor oil. The theory of the treatment was based on the fact that sodium ricinoleate is capable of neutralizing bacterial poisons. Vaccines which produce marked local reaction may be detoxified by the addition of sodium ricinoleate, so that little or no reaction follows intradermal injection. Capsules of sodium ricinoleate were employed in several cases in the hope that thereby dead bacteria in the intestines might be detoxified, furnishing a local antigen which might in turn aid in desensitization.

Clinically, the results have been good, although the authors state that their experience with the drug is still too limited to enable them to state what its ultimate value may be. Further investigations are being undertaken and will be reported at a later date. The dose is 5 grains of the drug in capsules three times a day.

Treatment of Eczema in Infants. Robinson, H. M.: South. M. J. **22**: 936, 1929.

In the experience of the writer, eczema in infants usually appears after the institution of a diet of cow's milk. The problem confronting the physician is the substitution of a milk-free diet without injury to the health of the patient. Such a diet is outlined and its effects noted upon eleven patients, one with urticaria pigmentosum and ten with eczema. Great reliance was placed upon cod liver oil as the main adjunct to a mixed diet. The cod liver oil was well tolerated both in winter and in summer.

Results showed immediate effects in four of the cases with partial or complete disappearance of the lesions. Four mothers found the régime too trying and gave up the diet. The remaining cases showed improvement of the lesions but the situation was complicated by failure of the patient to gain weight. This factor was the most discouraging in the treatment, as it involved worry on the part of the parent often causing her to discontinue the diet. Consistently good results were obtained in the majority of cases.

Specific Protein Reactions in Eye, Ear, Nose and Throat. Piness, G., and Miller, H.: Ann. Otol., Rhin., & Laryng. **38**: 691, 1929.

A discussion is presented by the authors, of the diagnosis, symptomatology, and treatment of allergy in relation to the respiratory system. Proper diagnosis rests upon a thorough pursuit of the family history, clinical history, physical examination, including that of nose and throat, skin tests, x-ray studies of the lungs and sinuses, and labora-

tory studies. In an allergic condition, any portion of the respiratory tract may present a mucous membrane lining in which the lymphoid tissue is hyperplastic, the mucous glands hypersecreting, and the tissue as a whole edematous. Proteins capable of producing such a condition are discussed at some length. Specific treatment is based upon the supposition that any particular protein that has given a positive skin reaction is etiologically important. In the case of pollen sensitivity, preseasonal treatment is advised, beginning about fourteen weeks prior to the expected period of onset. In the majority of cases of food sensitization, satisfactory results can be obtained by the elimination of the offending food protein from the diet. Individuals sensitive to the epidermals; i.e., fine epithelial scales from horse, dog, cat, chicken, goose, etc., may often be treated by avoidance of contact. When this is not possible, treatment similar to that for pollen sensitization, is indicated. When other methods of determining the etiology have failed and the case appears to be one of the bacterial type, results may be obtained by the use of stock or autogenous vaccines.

Considerable discussion is given to the consideration of operative measures. The belief is expressed that most sinus conditions in the allergic individual are merely coincidental or secondary to the existing allergic condition. Surgery, however, is advised whenever drainage or proper ventilation is interfered with. Polypi, if present, should be removed, and broadly speaking, all foci of infection should be eradicated for the general good of the patient. The otorhinolaryngologist, however, should realize that the removal of the sequelae will not affect the course of the allergic disease, and he should give symptomatic relief with the full realization that the underlying cause is not thus being influenced.

The Clinical Picture of Anaphylactic Ophthalmia with Observations on the Pathogenesis of Parenchymal Keratitis. Löwenstein, A.: Klin. Monatsbl. f. Augenh. **82:** 64, 1929.

In 1917, in a series of severe cases of trachoma, the author noticed acute inflammations of the cornea, which could not be brought into line with any of the known forms of keratitis. These observations led him to the definition of an anaphylactic keratitis in man. It was characterized by an acute dark red coloration of the eyeball and a smoky gray thickening of the parenchyma, hypotonia, severe pain, quick diminution of inflammation, and a residue of numerous speckled flakes in the clear portion of the cornea. This clinical picture he could not trace to any known infection. In support of a diagnosis of anaphylactic keratitis, the following theory was offered:

Subepithelial infiltration of the bulbus conjunctiva tunica and cicatrization in the pericorneal region lead to nutritional disturbances in the parenchyma of the cornea. The nutritional disturbance in the

sphere of the marginal network leads on the one hand to the picture of compensation vessels in the superficial vessels of the conjunctiva, in the form of the pannus. On the other hand, there is an antigenic resorption of the tissue of the cornea, the basis of the anaphylactic reaction. Renewed resorption from the one or the other eye then gives rise to the anaphylactic inflammation.

Three case reports are given in detail which deal with diagnosis, treatment, and prevention. Comment is made upon the anaphylactic stage of tuberculous iritis, as noted by Schieck and upon the reaction of the cornea which has been known to accompany an anaphylactic reaction to horse serum. It is suggested that anaphylactic symptoms occur in the eye more often than is commonly suspected.

Allergic Dermatoses and Their Treatment. Jessner, E.: Therap. d. Gegenw. **70**: 163, 1929.

The author lists those dermatoses which in his opinion may be considered as anaphylactic in nature: pruritus simplex, urticaria, prurigo, Quincke's edema, Henoch's purpura, eczema, and other atypical dermatoses. Of one of these, the eczema which Rost has described and brought into relationship with asthma, he writes in some detail. Before considering the questions of diagnosis and treatment, he enters into a lengthy discussion of the relationship between allergy and anaphylaxis. Diagnostic measures, such as skin tests, are dealt with in detail. Whenever it is possible to treat the allergic dermatoses by the elimination of the offending agent, such treatment is advised. In cases where this is not possible, desensitization must be attempted.

A Practical Application of the Method of Desensitization by Repeated Skin Reactions. Urticarial Reaction to Insulin. Jeannert, R.: Rev. méd. de la Suisse Rom. **49**: 99, 1929.

The author reports a case of severe urticaria following insulin treatment. Skin tests gave positive reactions to insulin. Control patients gave negative reactions. The possibility was considered that the patient might be sensitive to the particular animal component of that particular insulin product (Sandoz). Samples of insulin prepared from different kinds of animals—cow, horse, hog, sheep, etc.—were obtained and a skin test with Walker's technic was done with each type. The statement is made that all the reactions were positive and of about an equal intensity. The accompanying table, however, shows a range from a wheal 17 mm. in diameter (Roussep's insulin made from the pancreas of horse) to one of less than 4 mm. (Allen and Handbury's made from beef pancreas). As insulin treatment was necessary to the health of the patient, desensitization was undertaken by means of repeated skin tests. These were performed at two or three day intervals. The first fifteen reactions were clearly positive,

the sixteenth borderline, the seventeenth negative. The following three were again positive. The twenty-first was negative. From that point, Sandoz, Allen and Handbury, and Roche insulin were used alternately. The next six reactions were negative. The subcutaneous method was then employed. Each day, successive doses of 2, 4, 6, 8, 10 units of Sandoz insulin mixed with physiologic serum, were injected. After this course, 10 units of pure insulin were twice injected upon the same day with no ill effects to the patient. The patient was then able to undergo an insulin treatment of ten days with no recurrence of urticaria.

In view of his experience, the author states his belief that an intolerance to certain medicines is not always a contraindication to their administration, but only a reaction of the organism to which an adaptation may be made.

On Sensitivity to House Dust. Storm van Leeuwen, W., Krause, K., and Tissot van Patot, P. N.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **62**: 390, 1929.

The authors give a brief résumé of the American literature relating to the subject and then proceed to their own experiments. House dust is extracted according to the following formula: 1 gram house dust is ground in a mortar with 20 c.c. physiologic salt solution and then extracted for an hour at room temperature in a shaking machine. Then it is passed through a Berkefeld filter, tested for sterility and carbolized. This method is employed because of its simplicity and because it rules out the possibility of the presence of peptone or histamine-like products which might appear during extraction of greater length at a higher temperature. The extract is used in a dilution of 1:10. It is tested for negative reaction against normal individuals.

A simple skin test by intracutaneous injection of 0.1 c.c. of seven different dust extracts was made upon 25 allergic patients. The results showed that an asthmatic need not necessarily give the strongest reaction to his own house dust. Rather, it should be concluded that in general, there is house dust that is rich in allergen and house dust that is poor in allergen. A passive transfer was attempted upon 8 normal individuals who gave a negative reaction to house dust. The transfer succeeded in 7 out of the 8 cases. Four of the cases were injected with the serum of a sensitive patient W. A. A reaction, passively induced, was obtained in these cases not only to the house dust of W. A., but also to other house dusts. In a few cases desensitization was attempted with the passive transfer. Results showed that in most instances after desensitization with one house dust, another house dust called forth no reaction.

These observations seem to point to the fact that the house dusts employed in the foregoing experiments must contain a common aller-

gen which dominates the allergenic action of house dust extract. It is estimated that about 80 per cent of asthmatics in the region in which the authors live, are sensitive to house dust allergen.

On the Sensitivity of the Skin of Normal and Allergic Individuals to Nonallergens. Storm van Leeuwen, W., and van Niekerk, J.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **62**: 405, 1929.

A comparison in the reactions of normal individuals and of allergics to nonallergic substances is made. Care was taken to use the allergic patient only in periods when he was free from attack. Forty asthmatics and ten normal subjects were used. Sensitivity of the skin to intracutaneous injection of histamine 1:3000, of peptone 5:1000 and 1:1000 was investigated. The histamine injection was made always upon the front part of the left upper arm and the 1:1000 peptone on the front part of the right upper arm; the 5:1000 peptone on the front part of the left lower arm. Twenty minutes after the injection, measurement was made of the wheal and the surrounding erythema. Results show that the skin of allergic and of normal individuals responds quantitatively and qualitatively in the same manner.

Anaphylactic Crossed Relationship Between Horse Dander and Horse Serum. Ratner, B., and Gruehl, H. L.: Arch. Path. **8**: 635, 1929.

The paper is a substantiation of a preliminary report in 1925, in which the stand was taken that a cross anaphylactic relationship does exist between horse dander and horse serum. In the present work, protocols are given in detail. In general, the procedure was as follows:

All animals were normal and each animal was sensitized either to horse dander or horse serum and received a crossed injection of horse serum (or diphtheria antitoxin) or of horse dander extract. All animals not killed by the crossed shock injection, were given a second shock injection, one hour later, of the substance to which they were originally sensitized. Results were considered only in those animals in which sensitization was established. In all instances of death, the only criterion of anaphylaxis accepted was the fact of lungs fully distended after the wall of the chest was opened.

In the first group 65 guinea pigs of different sizes had received injections of horse serum varying from 0.2 to 10 c.c., given either intraperitoneally or intravenously. After an incubation period of from several weeks to seven months, each animal received an intravenous injection of from 0.5 to 1 c.c. of dander extract. Results showed 7 manifesting crossed anaphylaxis after receiving injections of dander extract. Fifty-eight gave negative results.

In Group 2, were 18 guinea pigs, each of which received intraperitoneally 0.1 c.c. normal horse serum. The animals were of practically

uniform weight. After an incubation period of seventeen days each received intravenously an injection of 1 c.c. dander extract. Only two showed crossed relationship to a moderate degree.

In Group 3, were 13 guinea pigs which were sensitized by intraperitoneal injection of 5 c.c. horse serum; i.e., fifty times the sensitizing dose of the previous group. Six animals showed a moderate anaphylaxis, thus demonstrating a higher degree of crossed sensitivity than in the previous group. In general, it was stated that when horse serum was used for the sensitizing dose, it was difficult to produce a crossed reaction with horse dander.

Strikingly different was the situation when the animals were sensitized to horse dander extract. In this series, of a total of 18 guinea pigs, 7 died in typical anaphylactic shock after the crossed injection of horse serum. Four showed definite anaphylaxis, 3 moderate symptoms, and only 4 gave negative reactions. This crossed relationship was also demonstrated by the Dale method of the uterine strip. Further Dale experiments were discontinued, as the authors did not consider it as dependable as the intravenous route for determining a given state of hypersensitiveness.

The crossed relationship between horse dander sensitization and diphtheria antitoxin was also studied, with evidence of a positive crossed reaction.

In a further series of experiments, 61 guinea pigs were sensitized through the inhalation of dry horse dander. Of this series, only 2 showed a definite crossed reaction with horse serum; 5 showed moderate symptoms and 8 gave suggestive reactions.

In a final series of 57 guinea pigs, the crossed relationship between horse dander inhaled as an antigen, and diphtheria antitoxin injected as a shock agent, was studied. One guinea pig died in anaphylactic shock after the injection of antitoxin, 1 showed marked anaphylaxis with recovery, 6 showed moderate symptoms, 2 were possibly suggestive.

In conclusion, the authors state that horse dander and horse serum are antigenically related, the common substance being present in small amounts and related to the globulin fraction. This common substance is apparently present in smaller amounts in horse dander than in horse serum, as it is easier to sensitize a guinea pig to horse dander and cause shock with horse serum than vice versa. These findings, while at variance with those of Longcope and his coworkers, check with those of Forster.

Allergic Studies in Ascarides Idiosyncracy. Jadassohn, W.: Arch. f. Dermat. u. Syph. **156**: 690, 1928.

The presence of ascarides can be dangerous for man in three ways, giving rise to symptoms through mechanical, pharmacologic, or aller-

gic channels. The present work concerns the third manner; i.e., the releasing of the allergic reaction. Cases are cited at some length to illustrate the fact that the allergic symptoms are to be traced not only to ascarides infection but also, especially in cases of asthmatics, to the presence of ascarides in the surrounding atmosphere. Such conditions may be found not infrequently in the laboratories of those who work with ascarides material. Sensitivity to ascarides proves to be remarkably widespread. Hegglin, in skin tests upon 257 patients showed a positive reaction in 80 per cent of those between two and forty years of age. Children under one year reacted negatively. In general, the degree of reactivity was less in older persons than in younger. Individuals who at one time had suffered an ascarides infection could react negatively. Whether or not individuals who had never been infected could react positively, could not be ascertained with accuracy, as it is possible to have had such an infection without being aware of it. An eczematous reaction could not be induced by the application of ascarides antigen.

Inquiry into the nature of the antigen (ascarides broth) brought out the fact that the substance calling forth the reaction was not a protein. The antigen was dialyzable. After dialysis of two to six days, a reaction could be obtained in a sensitive subject, with the dialysate. The antigen proved also to be proof against digestion with trypsin and pepsin.

Further inquiry into the nature of the allergic reaction led to research upon the serum of the patient, to determine the nature of such a substance as could be shown to react specifically with the antigen. One method was to attempt to show precipitins in the serum. Experiments with the serum of two strongly sensitive patients failed to show precipitins. No attempt was made to demonstrate any complement binding substance. Another method was to demonstrate the Prausnitz-Küstner phenomenon of passive transfer of the sensitivity from man to man. Detailed experiments along these lines were undertaken with the following results:

(1) Positive reactions were obtained with 5 different sera of strongly sensitive subjects.

(2) The application of antigen on one or two places on a normal skin into which the serum of a sensitive patient had been injected, caused a reaction at both sites, even when these sites were widely separated.

(3) The transfer of antibodies could be demonstrated to sensitize to horse ascaris as well as to human ascaris.

(4) Citrated blood could be substituted for the serum of the patient with positive results.

(5) The serum retained its power to sensitize after a week at ice box temperature, or in a saturation of ½ per cent phenol or 5 per cent

chloroform. Heating for one hour at 56° lessened its power but did not inhibit it.

(6) In answer to the question as to whether or not the antibody might be a protein, it could only be stated that after dialysis no antibody could be demonstrated in the dialysate while it could be shown to be in the fluid within the dialyzing bag. It showed itself resistant against digestion by pepsin and trypsin.

In a further analysis, attempts were made to show the effect of a mixture of antigen and antibody in vitro. In a series of experiments, it was shown that under such conditions (mixture in vitro) the serum loses its power to carry over sensitivity. The antigen, likewise, under certain quantitative adjustments, loses its power. A neutralization phenomenon can take place on a skin normally sensitive, or made sensitive by transfer, provided the sensitivity of the test spot is not too great nor too slight.

The article carries many drawings and detailed protocols.

Skin Reactions to Filtrates of Hemolytic Streptococci in Acute and Subacute Nephritis. Hansen-Pruss, O. C., Longcope, W. T., and O'Brien, D. P.: J. Clin. Investigation **7**: 543, 1929.

A study was made of the incidence and intensity of skin reactions to bouillon filtrates of hemolytic streptococci, in three groups of cases:

(a) Patients suffering from acute and subacute nephritis.

(b) Normal individuals and patients affected with miscellaneous conditions.

(c) Patients suffering from uncomplicated acute tonsillitis.

Eighteen strains of hemolytic streptococci were used, 13 of the beta type and 5 of the alpha type, grown in beef infusion peptone broth. For skin reactions, the filtrates were usually employed in dilutions of 1:100. When positive reactions were obtained with these dilutions, tests were made with 1:500, 1:1000, 1:2000 and occasionally 1:5000 dilutions. For each test 0.1 c.c. of the dilution was used. Stock bouillon in 1:100 dilution was used for control, and a Dick reaction with 1 S.T.D. of "toxin" was always made at the same time. The necessity is shown of using different dilutions of the filtrate to distinguish varying degrees of reactivity of the skin. Among the three groups all transitions were found from those who were practically insensitive to those who reacted vigorously to 1:2000 dilutions.

Results showed in group (a), patients suffering from acute and subacute nephritis, 81.4 per cent gave positive skin reactions and 66.6 per cent strongly positive reactions. Group (b), normal controls, 62 per cent gave positive skin reactions but only 25 per cent strongly positive reactions. Group (c), patients with acute tonsillitis, 95.4 per cent gave positive skin reactions but only 18.1 per cent were strongly positive.

A quantitative difference was shown in the skin reaction between many patients with nephritis and the average normal individual or the individual suffering from acute tonsillitis. It is suggested that the heightened skin reaction to the filtrates of hemolytic streptococci can be interpreted as allergic reactions and that many patients suffering from acute and subacute nephritis are highly allergic to some constituent of hemolytic streptococci or to substances elaborated by these organisms. Continued investigation upon the incidence of hemolytic streptococci infection at the onset, during the course and with exacerbations of acute and subacute glomerular nephritis, led the authors to the viewpoint that the relationship is too frequent and too close to be incidental. It is suggested that the development of acute diffuse glomerular nephritis in patients suffering from hemolytic streptococci infections, may be due to the action of the products of the growth of hemolytic streptococci upon previously sensitized kidney cells.

An Address on Thymic Asthma. Thursfield, H.: Canad. M. A. J. **20**: 239, 1929.

In investigating the evidence of the existence of "thymic asthma" the author asks four questions:

1. What is the evidence that enlargement of the thymus is a cause of grave dyspnea in infants?

2. What are the symptoms and signs which can be legitimately interpreted as evidence of the existence of a perilous enlargement?

3. What are the results of operative interference?

4. Is operation or some other form of treatment most desirable?

In answer to the first question, he gives the opinion that there is a thymic asthma but that it is an uncommon condition and does not comprise more than a small minority of cases of infantile dyspnea. It has often been held that in the cases of dyspnea associated with a quite moderate enlargement of the gland, there is evidence of a flattening of the trachea. To the author, the evidence is unconvincing. There are many cases where the flattening has been sought for and not found; there is no case within his experience where the flattening was sufficiently striking to make it probable as a cause of dyspnea. It has been shown experimentally that the degree of pressure necessary to produce flattening of the trachea is far in excess of anything likely to be exerted by a soft structure like the thymus. Lastly, the really large thymus glands are found in children who die suddenly without symptoms of dyspnea. The death is always a sudden cardiac failure.

The radiologic evidence of the existence of a shadow in the region of the thymus gland is not always certain. It has been shown that there occur shadows that simulate an enlargement of the thymus but which are caused by quite other structures. There is some clinical

evidence, however, connecting dyspnea with an enlargement of the thymus. A case is cited of Ollivier's of Paris, in which alarming attacks of dyspnea in an infant were cured by thymectomy. Other cases have been reported.

In answer to question 2, the symptoms are dyspnea, cyanosis, and stridor, protrusion of the manubium sterni, palpation of the enlarged gland as it rises above the sternal notch during inspiration, dullness to percussion extending beyond the manubrium in the first two intercostal spaces, especially to the left, and the radiographic shadow in the expected place. Most of these symptoms may be misleading and due to other causes.

The utmost care in diagnosis is urged before operative measures are taken. Even with correct diagnosis there is the alternative treatment of x-ray. This is recommended by the author for all cases except those of extreme urgency that permit of no delay, where operation is necessary.

Immunological Investigations in Tropical Sprue in Porto Rico. V. Skin Tests with Various Food Preparations. Weiss, C., and Mandry, O. C.: J. Immunol. **16**: 283, 1929.

It is the experience of physicians in Porto Rico, that sprue patients as a rule, get well and stay well if they remain on a special diet which includes foods very low in carbohydrates but rich in vitamins and proteins, with a limited amount of fats of a certain type. No satisfactory explanation has been given for the notable intolerance of sprue patients to carbohydrates and fats. The authors looked for a possible explanation of the gastrointestinal reactions, in the group of immunologic reactions known as food idiosyncrasies, although aware of the fact that thus far no known instance of hypersensitiveness to carbohydrates and fats has been recorded, and that these cannot function as antigens. It was considered possible that there might be some relationship to the well-known idiosyncrasies to chemical substances such as antipyrin, quinine, etc., in which specific skin reactions have been elicited.

A large variety of foods used in Porto Rico, including carbohydrates and fats as well as proteins, were tested by the scratch method. A group of 29 cases of sprue and 26 nonsprue control cases were used. The sprue cases were of four kinds: (1) Very severe cases. (2) Moderately severe cases. (3) Mild cases. (4) Recovered cases.

The results were negative both in the sprue and the control cases, indicating that the digestive symptoms of sprue patients are not due to specific sensitization to any food products.